CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-895

Generic Name: Sevoflurane Inhalation Liquid, 100%, 250mL

Sponsor: Baxter Healthcare Corporation

Approval Date: July 2, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 75-895

JUL 2 2002

Baxter Healthcare Corporation,
Anesthesia and Critical Care
Attention: Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

Dear Madam:

This is in reference to your abbreviated new drug application dated June 5, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Sevoflurane Inhalation Liquid, 100%, 250 mL.

Reference is also made to your amendments dated January 26, April 12, May 3, and October 2 & 31, 2001; January 9, March 26, March 28, April 8, May 14, 20, 24, and June 28, 2002. & July 2, 2002 JM 7/14/02

The listed drug product referenced in your application is subject to periods of patent protection which expire July 27, 2017, (Patent No. 5,990,176 and Patent No. 6,288,127) and July 9, 2018, (Patent No. 6,074,668). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Sevoflurane will not infringe on the above listed patents, or that the patents are otherwise invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately unless an action is brought prior to the expiration of forty-five (45) days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the agency that Baxter Healthcare Corp. (Baxter) complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement of the '127 and '668 patents was brought against Baxter within the statutory forty-five day period. You have informed us that Abbott Laboratories initiated patent infringement action on the '176 patent against you in United States District Court for the Northern District of Illinois (Abbott Laboratories and Central Glass Co., LTD. v. Baxter Pharmaceutical Products and Baxter Healthcare Corp., Civil Action No. 01C 1867 and Civil Action No. 00C 5939). You have

further informed us that the Civil Action No. 01C 1867 has been resolved with a Judgement in favor of Baxter Healthcare, and Civil Action No. 00C 5939 has been dismissed as moot.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sevoflurane 250 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Ultane®.

With respect to 180-day generic drug exclusivity, we note that Baxter Healthcare Corporation, Anesthesia and Critical Care was the first to submit a substantially complete ANDA with a Paragraph IV Certification. Therefore, with this approval Baxter Healthcare Corporation, Anesthesia and Critical Care is eligible for 180-days of market exclusivity. Such exclusivity will begin to run either from the date Baxter Healthcare Corporation, Anesthesia and Critical Care Begins commercial marketing of the drug product, or in the absence of marketing, from the date of a decision of a court finding the patent invalid or not infringed whichever event occurs earlier [Section 505(j)(5)(B)(iv)].

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patent invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The

Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 7/2/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-895

FINAL PRINTED LABELING

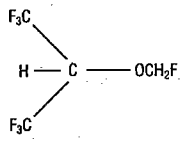
Sevoflurane

℞ only

Volatile Liquid for Inhalation

DESCRIPTION

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

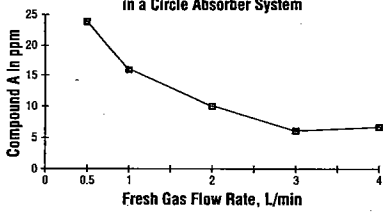
Sevoflurane is nonflammable and nonexplosive as defined by the requirements of International Electrotechnical Commission 601-2-13.

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 CO_2 absorbents (soda lime and Baralyme®) producing pentafluoroisopropenyl fluoromethyl ether, (PIFE, $C_4H_2F_6O$), also known as Compound A, and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether, (PMFE, $C_5H_6F_6O$), also known as Compound B.

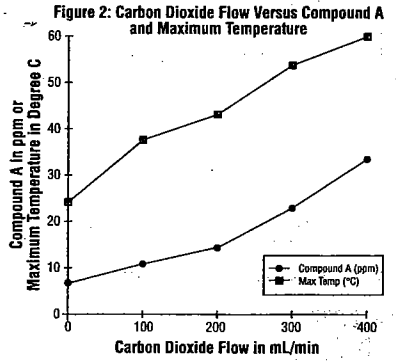
The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane similar to formation of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) from halothane. Baralyme causes 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 CO_2 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 CO_2 and Compound A production is illustrated in the following *in vitro* simulation where CO_2 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 CO_2 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 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 LC_{50} 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

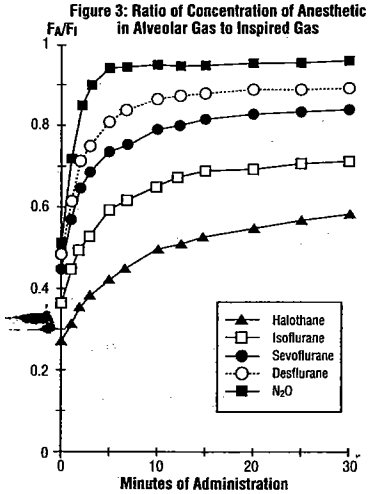
Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient @ 37°C = 0.63-0.69), a minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure. Therefore there is a rapid rate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

Induction of Anesthesia

In a study in which seven healthy male volunteers were administered 70% N_2O/30% O_2 for 30 minutes followed by 1.0% sevoflurane and 0.6% isoflurane for another 30 minutes the F_A/F_I 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.

F_A/F_I data from this study were compared with F_A/F_I 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.

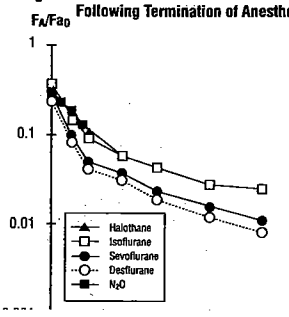
Figure 3: Ratio of Concentration of Anesthetic in Alveolar Gas to Inspired Gas



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 (F_A), relative to the last alveolar concentration (F_{a0}) 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.

Figure 4: Concentration of Anesthetic in Alveolar Gas Following Termination of Anesthesia



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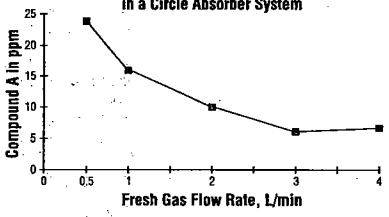

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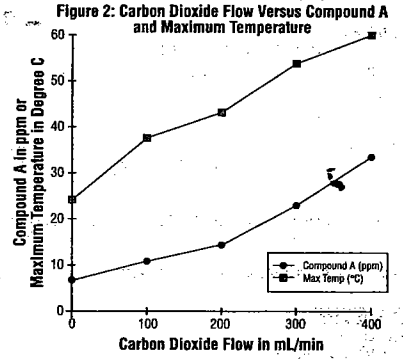

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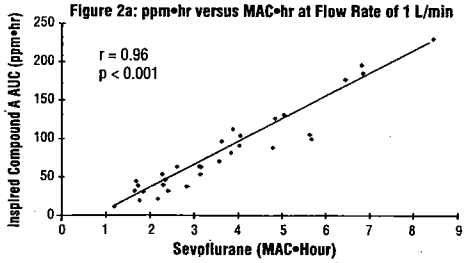
Figure 2a: ppm•hr versus MAC•hr at Flow Rate of 1 L/min



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F_A/F_I data from this study were compared with F_A/F_I 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.

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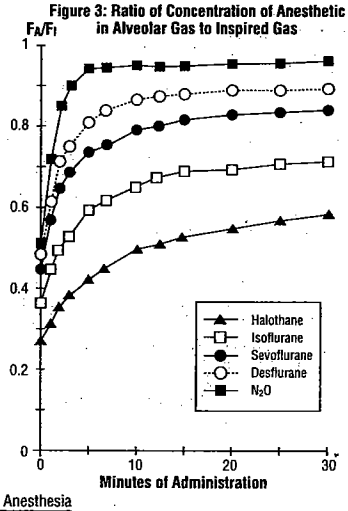

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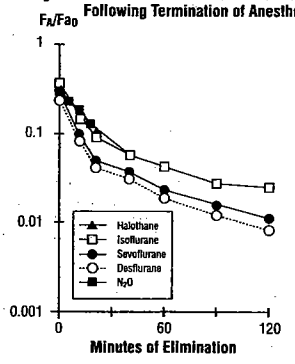

Yasuda N, Lockhart S, Eger EI II, et al: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72:316, 1991.

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 CO_2. 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.

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 N_2O 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/N_2O	Isoflurane/N_2O	Sevoflurane/N_2O	Propofol/N_2O
Mean Maintenance Anesthesia Exposure ± SD	0.64 ± 0.03 MAC•hr. (n=245)	0.66 ± 0.03 MAC•hr. (n=249)	0.8 ± 0.5 MAC•hr.(n=166)	7.3 ± 2.3 mg/kg/hr.(n=166)
Time to Emergence (min)	8.2 ± 0.4 (n=246)	9.3 ± 0.3 (n=251)	8.3 ± 0.7 (n=137)	10.4 ± 0.7 (n=142)
Time to Respond to Commands (min)	8.5 ± 0.4 (n=246)	9.8 ± 0.4 (n=248)	9.1 ± 0.7 (n=139)	11.5 ± 0.7 (n=143)
Time to First Analgesia (min)	45.9 ± 4.7 (n=160)	59.1 ± 6.0 (n=252)	46.1 ± 5.4 (n=83)	60.0 ± 4.7 (n=88)
Time to Eligibility for Discharge from Recovery Area (min)	87.6 ± 5.3 (n=244)	79.1 ± 5.2 (n=252)	103.1 ± 3.8 (n=139)	105.1 ± 3.7 (n=143)

n = number of patients with recording of recovery events.

Inpatient Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N_2O 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/N_2O	Isoflurane/N_2O	Sevoflurane/N_2O	Propofol/N_2O
Mean Maintenance Anesthesia Exposure ± SD	1.27 MAC•hr. ± 0.05 (n=271)	1.58 MAC•hr. ± 0.06 (n=282)	1.43 MAC•hr. ± 0.94 (n=93)	7.0 mg/kg/hr ± 2.9 (n=92)
Time to Emergence (min)	11.0 ± 0.6 (n=270)	16.4 ± 0.6 (n=281)	8.8 ± 1.2 (n=92)	13.2 ± 1.2 (n=92)
Time to Respond to Commands (min)	12.8 ± 0.7 (n=270)	18.4 ± 0.7 (n=281)	11.0 ± 1.20 (n=92)	14.4 ± 1.21 (n=91)
Time to First Analgesia (min)	46.1 ± 3.0 (n=233)	55.4 ± 3.2 (n=242)	37.8 ± 3.3 (n=82)	49.2 ± 3.3 (n=79)
Time to Eligibility for Discharge from Recovery Area (min)	139.2 ± 15.6 (n=268)	165.9 ± 16.3 (n=282)	148.4 ± 8.9 (n=92)	141.4 ± 8.9 (n=92)

n = number of patients with recording of recovery events.

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%).

Information regarding use of sevoflurane in pediatric patients undergoing elective repair or palliation of congenital heart disease is approved for Abbott Laboratories' ~~Ultane®~~ Sevoflurane. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled with this clinical trial information.

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 N_2O 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-N_2O was compared to isoflurane-N_2O for maintenance of anesthesia in a 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 N_2O-O_2-fentanyl anesthesia. During progressive hyperventilation from $PaCO_2$ = 40 to $PaCO_2$ = 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% O_2 or up to 70% N_2O/O_2. 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 should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents nor in 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 com-

Time to Emergence (min)	8.2 ± 0.4 (n=246)	9.3 ± 0.3 (n=251)	8.3 ± 0.3 (n=137)	10.4 ± 0.7 (n=142)
Time to Respond to Commands (min)	8.5 ± 0.4 (n=246)	9.8 ± 0.4 (n=248)	9.1 ± 0.7 (n=139)	11.5 ± 0.7 (n=143)
Time to First Analgesia (min)	45.9 ± 4.7 (n=160)	59.1 ± 6.0 (n=252)	46.1 ± 5.4 (n=83)	60.0 ± 4.7 (n=88)
Time to Eligibility for Discharge from Recovery Area (min)	87.6 ± 5.3 (n=244)	79.1 ± 5.2 (n=252)	103.1 ± 3.8 (n=139)	105.1 ± 3.7 (n=143)

n = number of patients with recording of recovery events.

Inpatient Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N_2O 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/N_2O	Isoflurane/N_2O	Sevoflurane/N_2O	Propofol/N_2O
Mean Maintenance Anesthesia Exposure ± SD	1.27 MAC•hr. ± 0.05 (n=271)	1.58 MAC•hr. ± 0.06 (n=282)	1.43 MAC•hr. ± 0.94 (n=93)	7.0 mg/kg/hr ± 2.9 (n=92)
Time to Emergence (min)	11.0 ± 0.6 (n=270)	16.4 ± 0.6 (n=281)	8.8 ± 1.2 (n=92)	13.2 ± 1.2 (n=92)
Time to Respond to Commands (min)	12.8 ± 0.7 (n=270)	18.4 ± 0.7 (n=281)	11.0 ± 1.20 (n=92)	14.4 ± 1.21 (n=91)
Time to First Analgesia (min)	46.1 ± 3.0 (n=233)	55.4 ± 3.2 (n=242)	37.8 ± 3.3 (n=82)	49.2 ± 3.3 (n=79)
Time to Eligibility for Discharge from Recovery Area (min)	139.2 ± 15.6 (n=268)	165.9 ± 16.3 (n=282)	148.4 ± 8.9 (n=92)	141.4 ± 8.9 (n=92)

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Non-Cardiac Surgery Patients At Risk For Myocardial Ischemia

Sevoflurane-N_2O was compared to isoflurane-N_2O 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 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% O_2 or up to 70% N_2O/O_2. 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

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CONTRAINDICATIONS

Sevoflurane can cause malignant hyperthermia. It should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents nor in 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% N_2O, 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-N_2O 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.

Potentiation 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 N_2O/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.

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences. Clinical judgement should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **ADVERSE REACTIONS**).

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 CO_2 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 alkalies (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 occured 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

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

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported. Histological evidence was not provided for any of the reported hepatitis cases. In most of these cases, patients had underlying hepatic conditions or were under treatment with drugs known to cause hepatic dysfunction. Most of the reported events were transient and resolved spontaneously (see **PRECAUTIONS**).

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

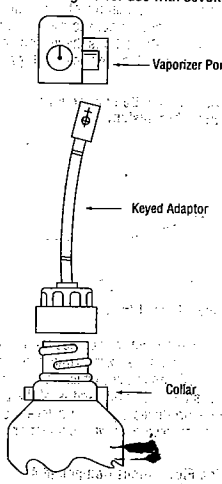
Age of Patient (years)	Sevoflurane in Oxygen	Sevoflurane in 65% N_2O/35% O_2
0 -1 months #	3.3%	
1 - <6 months	3.0%	
6 months - <3 years	2.8%	
3 - 12	2.5%	
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

Neonates are full-term gestational age. MAC in premature infants has not been determined.

@ In 1 - <3 year old pediatric patients, 60% N_2O/40% O_2 was used.

Directions for Filling Vaporizers

Sevoflurane is provided with a keyed bottle collar and should be filled only into vaporizers designed for use with sevoflurane using a keyed adaptor.



1. Remove the overseal and cap from the anesthetic bottle and ensure that the bottle neck is not damaged.
2. Place the large end of the adaptor over the collar, aligning the holes in the adaptor with the tabs on the collar, and tighten securely. The color of the adaptor must match the color of the collar for the adaptor to index properly.
3. Attach the other end of the adaptor to the filling port of the vaporizer in accordance with the vaporizer manufacturer's instructions and fill the vaporizer.
4. Disconnect the adaptor from the vaporizer and allow any excess sevoflurane to drain back into the bottle before disconnecting the adaptor from the bottle.
5. Replace the cap securely on the bottle.

HOW SUPPLIED

Sevoflurane, Volatile Liquid for Inhalation, is available as:

NDC 10019-651-64 - Aluminum bottle containing 250 mL sevoflurane.

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 N_2O).

Storage

Store at controlled room temperature 15°-30°C (59°-86°F) [see USP].

The bottle cap should be replaced securely after each use of sevoflurane.

Ultane is a registered trademark of Abbott Laboratories. deleted

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Baxter Healthcare Corporation of Puerto Rico
Guayama, Puerto Rico 00784

For Product Inquiry 1 800 ANA DRUG
(1-800-262-3784)

Revised: June 2002 460-220-06

underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **ADVERSE REACTIONS**).

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 CO_2 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 alkalies (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 occured 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

Adverse Events During Post-Marketing Experience: 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 occured during, or soon after sevoflurane induction, during emergence, and during post-operative recovery up to a day following anesthesia.

...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.

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3 - 12	2.5%	
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

APPROVED JUL - 2 2002

Neonates are full-term gestational age. MAC in premature infants has not been determined.

@ In 1 - <3 year old pediatric patients, 60% N_2O/40% O_2 was used.

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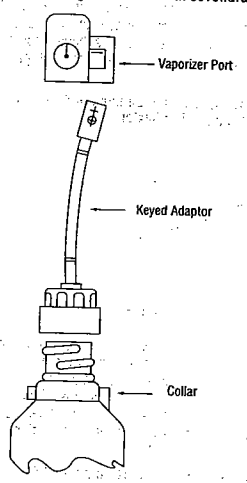

1. Remove the overseal and cap from the anesthetic bottle and ensure that the bottle neck is not damaged.
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3. Attach the other end of the adaptor to the filling port of the vaporizer in accordance with the vaporizer manufacturer's instructions and fill the vaporizer.
4. Disconnect the adaptor from the vaporizer and allow any excess sevoflurane to drain back into the bottle before disconnecting the adaptor from the bottle.
5. Replace the cap securely on the bottle.

FINAL - 2 2002

HOW SUPPLIED

Sevoflurane, Volatile Liquid for Inhalation, is available as:

NDC 10019-651-64 - Aluminum bottle containing 250 mL sevoflurane.

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 N_2O).

Storage

Store at controlled room temperature 15°-30°C (59°-86°F) [see USP].

The bottle cap should be replaced securely after each use of sevoflurane.

Ultane is a registered trademark of Abbott Laboratories. deleted

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Baxter Healthcare Corporation of Puerto Rico
Guayama, Puerto Rico 00784

For Product Inquiry 1 800 ANA DRUG
(1-800-262-3784)

Revised: June 2002 7

460-220-06

BAXTER PPI

Sevoflurane Inhalation Anesthetic

250 mL [Aluminum] bottle label

Code: 460-263-00

460-263-00

Contains sevoflurane 250 mL.
For inhalation anesthesia.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) [see USP].
For Product Inquiry 1 800 ANA DRUG.
(1-800-262-3784)

NDC 10019-651-64

Sevoflurane

Inhalation Anesthetic

250 mL **Rx only**

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Baxter Healthcare Corporation of Puerto Rico
Guayama, Puerto Rico 00784

N 3 10019 65164 4

Lot:

Exp. Date:

460-263-00 Sevoflurane 250 mL Bottle Label (For Aluminum Bottle)
Size: 3" x 6 5/8" Corner: 1/8"
USA
Submission - 1 12/12/2000

Approved by:

_____ (Baxter Packaging) _____ Date

_____ (Baxter QA) _____ Date

PMS 109 Canary Yellow
= Horizontal Band.

PMS 287 Baxter Blue
= All Other Text and Bar Codes.

Guide Line
= DO NOT PRINT.

Dotted Line
= Indicate Imprint Area. DO NOT PRINT.

Full UV Varnish.

APPROVED
JUL 2 2002

NDC 10019-651-60

Sevoflurane

Inhalation Anesthetic

250 mL **℞ only**

Baxter

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Baxter Healthcare Corporation of Puerto Rico
Guayama, Puerto Rico 00784

Contains sevoflurane 250 mL.
For inhalation anesthesia.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) [see USP].
For Product Inquiry 1 800 ANA DRUG
(1-800-262-3784)

460-218-01

N 3 10019 65160 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-895

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 75-895

FIRM: Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence NJ 07974

DOSAGE FORM: Liquid for Inhalation STRENGTH: 250 mL

DRUG: Sevoflurane

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 11/27/00.

BIO STUDY INFORMATION: Waiver found acceptable 09/28/00.

METHODS VALIDATION: Pending.

STABILITY:

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in both containers.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	LIMIT	METHOD
Appearance	Clear Colorless liquid	Visual inspection
	NMT	USP <921>
	NMT	PF monograph
pH	5.0-7.5	USP <791>
Nonvolatile Residue	NMT (w/v) NMT	PF Monograph
	NMT	PF Monograph
Assay Sevoflurane	NLT	GK1134
	NMT	GK1134
	NMT	GK1134
	NMT	GK1134
Compound A	NMT	GK1134
Individual Others	NMT	GK1134
Total Impurities	NMT	GK1134

The firm seeks 24 month expiration dating based on the submitted stability data. Accelerated and room temperature stability data were submitted for the product packaged in each market container. Bottles were stored upright and horizontally. All data were within the stated specifications. There was a slight [redacted] but was well within the specification limit of NMT [redacted]

LABELING: Acceptable 5/16/01 per review by C.Park.

STERILIZATION VALIDATION: NA

SIZE OF BIO BATCH: NA: Waiver was requested. Decision based on information submitted for test batch equivalent to [redacted]

SIZE OF STABILITY BATCHES: A copy of the executed batch record for exhibit batch #SR1201-9902 [redacted] begins on p. 622. The production of batch involves the repetition of various, [redacted]. A control record for each step is generated. The overall process consists of about 10 control records. Conversion yields are indicated after each step.

PROPOSED PRODUCTION BATCH:
The intended production batch size is [redacted] equivalent to [redacted] bottles.

RECOMMENDATION: Approve.

SIGNATURE: [S] DATE: 12/18/01

APPEARS THIS WAY
ON ORIGINAL

COMPONENTS AND COMPOSITION

There are no inactive ingredients in the drug product formulation. The drug product consists of the drug substance only.

Component	RLD	Baxter PPI
Sevoflurane	100%	100%
Inactive Ingredients	None	None

The final product tests and specifications are as follows:

TEST	LIMIT	METHOD
Appearance	Clear Colorless liquid	Visual inspection
Identification	Infrared spectra of sample and std exhibit maxima at same wavelengths	USP <197>
Volume in Container	NLT label claim	USP <1>
[redacted]	NMT [redacted]	USP <921>
[redacted]	NMT [redacted]	PF monograph
[redacted]	NMT [redacted]	USP <221>
pH	5.0-7.5	USP <791>
Nonvolatile Residue	NMT [redacted] (w/v) NMT [redacted]	PF Monograph
[redacted]	NMT [redacted]	PF Monograph
[redacted]	[redacted]	USP <831>
Assay Sevoflurane	NLT [redacted]	GK1134
[redacted]	NMT [redacted]	GK1134
[redacted]	NMT [redacted]	GK1134
[redacted]	NMT [redacted]	GK1134
Compound A	NMT [redacted]	GK1134
Individual Others	NMT [redacted]	GK1134
Total Impurities	NMT [redacted]	GK1134

The COA for lot #S001C003E manufactured March of 2000 is provided on p. 987.

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-895

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceutical Products Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence NJ 07974

4. LEGAL BASIS FOR SUBMISSION
Ultane ® Abbott Laboratories
Paragraph IV certification, lawsuit filed.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sevoflurane

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission June 5, 2000

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Liquid for Inhalation

14. POTENCIES
250 mL

15. CHEMICAL NAME AND STRUCTURE
fluoromethyl 2,2,2-triflouro-1-trifluoromethyl)ethyl ether].

17. COMMENTS
Chem, label, MV pending. First Generic.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable minor.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
10/30/00

Redacted 16

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-895

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceutical Products Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence NJ 07974

4. LEGAL BASIS FOR SUBMISSION
Ultane ® Abbott Laboratories
Paragraph IV certification, lawsuit filed.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sevoflurane

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission June 5, 2000
Amendment Jan 26, 2001

10. PHARMACOLOGICAL CATEGORY
Anesthetic

11. Rx or OTC
RX

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Liquid for Inhalation

14. POTENCIES
250 mL

15. CHEMICAL NAME AND STRUCTURE
fluoromethyl 2,2,2-triflouro-1-trifluoromethyl)ethyl ether].

17. COMMENTS
Chem, label, MV pending. First Generic.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable.

19. REVIEWER:
A.Langowski

DATE COMPLETED:
02/28/01

Redacted 19

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-895

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceutical Products Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

4. LEGAL BASIS FOR SUBMISSION
Ultane ® Abbott Laboratories
Paragraph IV certification, lawsuit filed.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sevoflurane

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission June 5, 2000
Amendment Jan 26, 2001
Amendment 4/12/01

10. PHARMACOLOGICAL CATEGORY
Anesthetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Liquid for Inhalation

14. POTENCIES
250 mL

15. CHEMICAL NAME AND STRUCTURE
fluoromethyl 2,2,2-triflouro-1-trifluoromethyl)ethyl ether].

17. COMMENTS
MV pending. First Generic.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable; Facsimile.

19. REVIEWER: A.Langowski

DATE COMPLETED: 05/15/01; 09/20/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 21

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-895

3. NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceutical Products Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

4. LEGAL BASIS FOR SUBMISSION
Ultane ® Abbott Laboratories
Paragraph IV certification, lawsuit filed.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sevoflurane

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission June 5, 2000
Amendment Jan 26, 2001
Amendment 4/12/01
Amendment 10/31/01
Amendment 03/26/02
Amendment 04/08/02

10. PHARMACOLOGICAL CATEGORY
Anesthetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Liquid for Inhalation

14. POTENCIES
250 mL

15. CHEMICAL NAME AND STRUCTURE
fluoromethyl 2,2,2-triflouro-1-trifluoromethyl)ethyl ether].

17. COMMENTS
MV pending. First Generic.

18. CONCLUSIONS AND RECOMMENDATIONS
Approve.

19. REVIEWER: A.Langowski

DATE COMPLETED: 11/19/01

APPEARS THIS WAY
ON ORIGINAL

Redacted 24

Page(s) of trade secret and /or confidential commercial information

ADDENDUM

ANDA # 75-895 REVIEW # 4

NAME AND ADDRESS OF APPLICANT
Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, NJ 07974

PROPRIETARY NAME	NONPROPRIETARY NAME
NA	Sevoflurane

AMENDMENT DATE: March 26, 2002

COMMENTS
The firm was asked to verify the —— specification for the drug product for release and stability was NMT ——————

The firm submitted copies of the regulatory specifications and the stability protocol confirming the above —— specification.

CONCLUSIONS AND RECOMMENDATIONS
The application may be approved.

REVIEWER:	DATE COMPLETED:
Glen Jon Smith	March 27, 2002
Team Leader	
Team 9	

3/27/02

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-895

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-895 SPONSOR : Baxter Pharmaceutical

DRUG AND DOSAGE FORM: Sevoflurane Inhalation Solution, USP, 100%

STRENGTH(S) : 10 mg/mL

TYPES OF STUDIES : NA

CLINICAL STUDY SITE(S) : NA

ANALYTICAL SITE(S) : NA

STUDY SUMMARY : **NA**

DISSOLUTION : NA

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic NO New facility ___ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : Zakaria Z. Wahba DATE : 8/25/00

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 8/25/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 9/28/00

BIOEQUIVALENCY COMMENTS

ANDA: #75-895 APPLICANT: Baxter Pharmaceutical

DRUG PRODUCT: Sevoflurane Inhalation Solution, USP, 100%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Sevoflurane Inhalation Solution, USP 100%
ANDA # **75-895**
Reviewer: Z.Z. Wahba
V:\firmsam\baxter\ltrs&rev\75895w.600

Baxter Pharmaceutical
New Providence, NJ
Submission Date:
June 05, 2000

REVIEW OF A WAIVER REQUEST

BACKGROUND

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Sevoflurane Inhalation Solution, USP, 100%. The RLD is Ultane® Inhalation Solution, 100% (Abbott, NDA #20-478).

2. Sevoflurane is an inhalation agent for induction and maintenance of general anesthesia. It is indicated for used by trained medical professional only.

3. Sevoflurane is a solution marketed in 250-mL bottles. The solution is vaporized using a vaporizer. The product labeling suggests that no specific vaporizer is recommended for the RLD. Therefore, from the bioequivalence stand point, this product should be evaluated in the same manner as other inhalation solutions used with vaporizers (nebulizers), e.g. albuterol inhalation solution. In the past, DBE has requested Q1 and Q2 sameness of the test and reference products of albuterol inhalation solutions (ANDAs #[redacted] #[redacted] #75-358, #75-343, #75-063 and #[redacted]). Those products were approved on the basis of waivers of *in vivo* bioequivalence study requirements under 21 CFR Section 320.22 of Bioavailability/Bioequivalence Regulations.

FORMULATION COMPARISON

Comparative compositions of the test and the reference Abbott's Ultane® Inhalation Solution, 100%, products are as follows:

Comparison of Formulation
(Not to be released under FOI)

Ingredient	Test Product (potency)	RLD (potency)
Sevoflurane	100%	100%
Additives/Inactive ingredients	None	None

Sevoflurane inhalation solution USP is a clear, colorless, stable

liquid containing no additives or chemical stabilizers, and has a target pH of ——

COMMENTS

1. The firm's test solution product is identical, qualitatively and quantitatively, to the innovator product.

2. The waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR section 320.22(b)(2) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Baxter Pharmaceutical demonstrates that Sevoflurane Inhalation Solution, USP, 100%, falls under 21 CFR Section 320.22(b)(2) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for Sevoflurane Inhalation Solution, USP, 100%, of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test solution formulation to be bioequivalent to Abbott's Ultane® Inhalation Solution, 100%.

The firm should be informed of the recommendation.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

bmd 8/25/00

RD INITIALED BDAVIT Barbara M David Date 8/25/00
FT INITIALED BDAVIT

Concur: Dale P. Conner Date 9/28/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #75-895
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer (Z. Wahba)
HFD-658/ Team Leader (B. Davit)

Endorsements:
HFD-658/ Z. Wahba Z.W. 8/25/00
HFD-655/ G. Singh GOPS 8/25/00
HFD-658/ B. Davit BD 8/25/00
HFD-650/ D. Conner DR 9/28/00

V:\firmsam\Baxter\ltrs&rev\75895w.600

BIOEQUIVALENCY - ACCEPTABLE submission date: 06/05/2000

1. **Waiver (WAI)** Strengths: **100%**
Outcome: AC

OUTCOME DECISIONS: AC - Acceptable
WINBIO COMMENTS: Acceptable Biostudy

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-895

CORRESPONDENCE

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

Via Facsimile and Airborne overnight Express

May 24, 2002

ANDA filed with Paragraph 4 Certification

NEW CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copy: Mr. Jeen Min, OGD Project Manager

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Certification of new Hatch-Waxman Exclusivity awarded to RLD, Ultane®

Dear Mr. Buehler,

Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] hereby submits certification to acknowledge the 3-year Hatch-Waxman exclusivity awarded to Ultane®, code M17 - Information regarding use of Ultane in pediatric patients with congenital heart disease, that expires on March 30, 2004 (reference electronic *Orange Book* dated May 15, 2002, copy attached). Baxter Healthcare, A&CC also certifies that its labeling for sevoflurane - liquid for inhalation will not contain the exclusive language until the expiration of the subject exclusivity.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

PJambhekar

Priya Jambhekar
Director, Regulatory Affairs

RECEIVED
MAY 2 8 2002
OGD / CDER

enc: Form FDA 356h
Relevant page from the electronic *Orange Book* dated May 15, 2002

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

Via Airborne overnight Express

May 20, 2002

ANDA filed with Paragraph 4 Certification

ORIG AMENDMENT
N/AF

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Mr. Chan Park, OGD - Division of Labeling

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: Submission of Revised Final Printed Package Insert Labeling

Dear Mr. Buehler:

Reference is made to the above-referenced pending ANDA for Sevoflurane – Liquid for Inhalation, submitted on June 5, 2000. Reference is also made to the teleconference of May 15, 2002 between Mr. Chan Park, Division of Labeling, OGD, and Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC], and to the confirmatory facsimile from Mr. Park (copy enclosed). As requested by Mr. Park, Baxter Healthcare, A&CC has revised the final printed package insert to replace the information in the 2nd paragraph of the CLINICAL PHARMACOLOGY (Clinical Trials, Pediatric Anesthesia) subsection ("Sevoflurane … cardiopulmonary bypass."), as follows:

> "Information regarding use of sevoflurane in pediatric patients undergoing elective repair or palliation of congenital heart disease is approved for Abbott Laboratories' Ultane®. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled with this clinical trial information.".

In addition, a typographical error in the x-axis of Fig 2 (March 29, 2002 telecon between Mr. Park and Baxter Healthcare, A&CC) has been corrected; the title of the x-axis is revised to: "Carbon Dioxide Flow in mL/min" (from ".. ———). Lastly, disclosure that "Ultane" is a registered trademark of Abbott Laboratories has been added. There are no other revisions. Copies of the package insert, annotated to show the above revisions, are also enclosed.

RECEIVED

MAY 2 1 2002

OGD / CDER

Baxter Healthcare, A&CC herewith submits fourteen [14] sets of revised final printed package insert labeling, which incorporates the requested statement, as follows: twelve [12] sets in the Archival copy, and two [2] sets in the Review copy.

Baxter Healthcare, A&CC believes this submission completes all requirements for final approval of this product. Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Final Printed Package Insert, code 460-220-06, rev. 4-02

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

May 14, 2002

***Via* Fax**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Mr. Chen Park, OGD - Division of Labeling
Mr. Adolph Vezza, OGD Labeling Team Leader

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Confirmation of revisions to Final Printed Package Insert Labeling

Dear Mr. Buehler:

Reference is made to the above-referenced pending ANDA for Sevoflurane – Liquid for Inhalation, submitted on June 5, 2000. Reference is also made to the teleconference of this morning between Mr. Adolph Vezza, Labeling Team Leader, OGD, and Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] in which Mr. Vezza dictated the following carve-out statement to replace the information in the 2nd paragraph of the CLINICAL PHARMACOLOGY (Clinical Trials, Pediatric Anesthesia) subsection (Sevoflurane … cardiopulmonary bypass.) with the following text:

> "The information regarding use of sevoflurane in pediatric patients with congenital heart disease is approved for Abbott Laboratories' Ultane®. However, due to Abbott's marketing exclusivity rights, this drug product is not labeled for use in pediatric patients with congenital heart disease."

Baxter Healthcare, A&CC would appreciate immediate notification if there are any additional revisions to the labeling or if Baxter Healthcare, A&CC is in error in its understanding. Baxter Healthcare, A&CC plans to submit revised final printed Package Insert labeling during this week.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

RECEIVED
MAY 16 2002
OGD / CDER

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Priya Jambhekar
Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence NJ 07974
tel: 908/286-7215 *fax*: 908/286-7269

Baxter

To: **Mr. Gary Buehler, OGD** **Fax #: 301/443-3847**
Mr. Adolph Vezza, OGD Labeling Review Branch

At: **FDA - OGD (HFD-600)**

Pages: 2 (including cover) **Date: 5/14/02**

☑ URGENT ☐ For Review ☐ As requested ☐ Please Comment ☑ Please Reply

---

- **Subject: ANDA 75-895: Sevoflurane, Liquid for Inhalation**
  Confirmation of revision to Final Printed Package Insert Labeling

Dear Mr. Buehler and Mr. Vezza,

The following page contains copy of a letter requesting confirmation of the requested revision to the package insert.

If you have any questions, please call me at 908/286-7215 or fax me at 908/286-7269. Thank you!

AB

for Priya Jambhekar
Director, Regulatory Affairs

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

April 18, 2002

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

NEW CORRESP

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
General Correspondence:* *Authorization for Mr. Robert Pollack to contact the Agency on behalf of Baxter Healthcare Corporation

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000.

Baxter Healthcare, A&CC herewith submits a Correspondence to the pending ANDA, to provide authorization for:

Mr. Robert Pollack, Vice President
Lachman Consultant Services Inc.
1600 Stewart Avenue
Suite 604
Westbury NY 11590,

to contact FDA, on behalf of Baxter Healthcare, A&CC, regarding this application.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

RECEIVED
APR 1 9 2002
OGD / CDER

cc: Mr. Robert Pollack (Lachman)

enc: Form FDA 356h

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Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

April 8, 2002

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

ORIG AMENDMENT

N/FA

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Dr. Andrew Langowski, Chemist, OGD Division of Chemistry I

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: CMC (Response to telecon of 4/8/02)

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000. Reference is also made to the minor amendment submitted on January 26, 2001.

Pursuant to a telephone request today from Dr. Andrew Langowski, Baxter Healthcare, A&CC, is resubmitting a copy of the sevoflurane drug substance specification, RS API 32D, which was originally submitted to this ANDA on January 26, 2001 (page 180).

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

RECEIVED

APR 0 9 2002

OGD / CDER

enc: Form FDA 356h
Resubmitted Specification and Stability Testing Protocol

G:\REGULATE\DOMESTIC\SEVOFLRN\FDA Corres\4-8-02 CMC Tel Amdt cvr.doc

Regulatory Affairs

Baxter Pharmaceutical Products Inc. 908.286.7000
95 Spring Street
New Providence, New Jersey 07974

Baxter

NEW CORRESP
NC
MAE mtk 4-3-02

March 27, 2002

Via *Fax and Airborne overnight Express*

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

Attention: Mr. Gary J. Buehler, Director
Office of Generic Drugs (HFD-600)

Desk copy: Mr. Jeen Min, Project Manager, OGD

re: **ANDA 75-895; Sevoflurane: Liquid for Inhalation**
Supplemental Notification of Court Decision

Dear Mr. Buehler:

This letter supplements our letter dated March 25, 2002, relating to the aforementioned ANDA, submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000. In order to avoid any confusion about the listed Paragraph IV certifications, Baxter Healthcare, A&CC provides the following supplemental explanation.

The only pending lawsuit relating to Baxter Healthcare, A&CC's amended ANDA (Docket No. 01C 1867) has now been resolved with a Judgment in favor of Baxter Healthcare, A&CC, that Baxter's proposed sevoflurane product in an aluminum container does not infringe Abbott's U.S. Patent No. 5,990,176, either literally or under the doctrine of equivalents. The other pending lawsuit (Docket No. 00C 5939), which has now also been resolved in favor of Baxter, relates to Baxter Healthcare A&CC's prior, and now withdrawn, proposed sevoflurane product in a — container. On March 26, 2002, that other lawsuit was resolved with the grant of Baxter Healthcare, A&CC's motion to dismiss the case as moot because of the withdrawal of the proposed product in a — container by Baxter Healthcare, A&CC's Amendment dated October 2, 2001. That lawsuit (Docket No. 00C 5939), which is now dismissed, does not relate to the product in Baxter Healthcare, A&CC's amended ANDA.

In summary, the *Orange Book* lists three (3) patents, 5,990,176 ('176), 6,074,668 ('668), and 6,288,127 ('127) under this Abbott NDA. Baxter Healthcare, A&CC's ANDA includes Paragraph IV certifications for each of these three patents. The '176 patent is the only patent involved in a lawsuit (Docket No. 01C 1867) involving Baxter Healthcare, A&CC's

amended ANDA. That lawsuit has now been resolved with a decision by the court that the '176 patent is not infringed, and therefore the provisions in 21 U.S.C. § 355 (j)(5)(B)(iii) requiring expiration of the thirty month period before approval of Baxter Healthcare's amended ANDA are no longer applicable. As evidence of the court's decision, attached is a copy of the Memorandum Opinion and Order and a copy of the Judgment In A Civil Case, which were entered in Case No. 01C-1867 on March 22, 2002. Also attached is a copy of the Memorandum Opinion and Order entered in Case No. 00C-5939 on March 26, 2002, granting Baxter Healthcare, A&CC's motion to dismiss.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Pharmaceutical Products Inc. 908.286.7000
95 Spring Street
New Providence, New Jersey 07974

Baxter

March 26, 2002

NDA

AMENDMENT

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Mr. Glenn Smith, Team Leader - OGD Division of Chemistry I

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: CMC (Response to telecon of 3/26/02)

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000, and amended on January 26, April 12, May 3, October 2, and October 31, 2001. Reference is also made to the Telephone Amendment submitted on January 9, 2002, in response to a request by Dr. Rashmikant Patel, Director – OGD Division of Chemistry I, to confirm that the release and stability specifications for — content of the product packaged in aluminum bottles are established at Not More Than [NMT] —

Pursuant to a telephone request today from Mr. Glenn Smith, Team Leader - OGD Division of Chemistry I, we are resubmitting a copy of the specification, RS FP 44D, and the Sevoflurane Marketed Product Stability Testing Protocol. As stated in the finished product regulatory specification, RS FP 44D, Sevoflurane Drug Product (Aluminum Bottle), [Ref: page 0297 of the January 26, 2001 Minor Amendment (which included information on the 250 mL aluminum bottles)], the stability testing protocol [Ref: page 0303 of the same amendment], and page 6 (response to comment 3) in the October 31, 2001 second minor amendment, Baxter Healthcare, A&CC confirms that the specifications for the allowable — content in the sevoflurane finished product at product release and shelf life (stability) testing are established at NMT —

RECEIVED

MAR 27 2002

OGD / CDER

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Resubmitted Specification and Stability Testing Protocol

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Pharmaceutical Products Inc. 908.286.7000
95 Spring Street
New Providence, New Jersey 07974

Baxter

March 26, 2002

NEW CORRESP

***Via* Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Chen Park, Office of Generic Drugs [OGD] - Division of Labeling

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
General Correspondence: Printer's Proof of Final Printed Package Insert

Dear Mr. Park,

Reference is made to the above-mentioned ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000, and amendments of April 12, May 3, and October 2, 2001, and January 9 and March 26, 2002.

Reference is also made to your telephone conversation with me this morning. As discussed, we are submitting two (2) sets of printer's proofs, code 460-220-05 revised October 2001, of the package insert, which are identical to the *draft* labeling submitted on October 31, 2001. I trust that this allows you to initiate your final review of the package insert labeling. Twelve (12) copies of the final printed labeling will be submitted under separate cover as soon as they are available.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Pjambhekar

Priya Jambhekar
Director, Regulatory Affairs

RECEIVED
MAR 27 2002
OGD / CDER

enc: Form FDA 356h

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

March 19, 2002

Via *Fax and Airborne overnight Express*

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

Attention: Mr. Gary J. Buehler, Director
Office of Generic Drugs (HFD-600)

Desk copy: Mr. Jeen Min, Project Manager, OGD

NEW CORRESP

re: **ANDA 75-895; Sevoflurane: Liquid for Inhalation**
45-Day Notification for Patent 6,288,127 ['127 Patent]

Dear Mr. Buehler:

Reference is made to the aforementioned ANDA, # 75-895, submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000. On January 22, 2002, Baxter Healthcare, A&CC submitted under this ANDA a Paragraph IV certification against '127 patent, and on February 4, 2002, submitted notification of receipt of the Baxter Healthcare, A&CC Paragraph IV certification by the patent holders. As indicated in the February 4, 2002 letter, Baxter Healthcare, A&CC sent notice of the Paragraph IV certification to Abbott Laboratories Inc. [Abbott] (patent and application holder) and Central Glass Co. Ltd. [Central Glass] (patent holder) by letter dated January 23, 2002. Abbott received the January 23, 2002 notice of the paragraph IV certification against the '127 patent on January 25, 2002 and Central Glass received such notice on January 29, 2002.

Pursuant to 314.107(f)(3), Baxter Healthcare, A&CC herewith submits a letter dated March 11, 2002 from R. Mark McCareins Esq., of the law firm, Winston & Strawn, sent on behalf of his clients, Abbott and Central Glass in response to the January 23, 2002 notice.

Abbott and Central Glass have not filed an action for patent infringement regarding the '127 patent within 45 days of receipt of the notice of paragraph IV certification.

RECEIVED

MAR 20 2002

OGD / CDER

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Copy of letter from Winston & Strawn

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

Return Receipts
OAI
PM
2/5/02

NEW CORRESP
NC

February 4, 2002

Via *Fax and Airborne overnight Express*

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

Attention: Mr. Gary J. Buehler, Director
Office of Generic Drugs (HFD-600)

Desk copy: Mr. Jeen Min, Project Manager, OGD

re: **ANDA 75-895; Sevoflurane: Liquid for Inhalation**
Correspondence to Pending ANDA - submission of the evidence of the receipt of paragraph IV notification by patent holders

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 05 2002
OGD

Dear Mr. Buehler:

Reference is made to the aforementioned ANDA, submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000. On January 22, 2002, Baxter Healthcare, A&CC submitted under this ANDA a Paragraph IV certification against Patent 6,288,127 ['127 Patent], assigned jointly to Abbott Laboratories [Abbott] and Central Glass Co. Ltd. [Central Glass]. Please note that the subject '127 patent is a continuation patent to the original patent 5,990,176 ['176 patent], for which Baxter Healthcare, A&CC has previously filed a Paragraph IV certification.

As required under 21 CFR 314.95 (b), on January 23, 2002, the law firm of Sidley Austin Brown & Wood notified *via* US Certified Return Receipt Requested mail to Abbott and Central Glass, on behalf of Baxter Healthcare, A&CC, of the filing of a Paragraph IV certification for '127 patent to the above mentioned ANDA for sevoflurane. A copy of the notification letter sent to Abbott and Central Glass is enclosed as Attachment 1.

OAI
gm 2/13/02

According to 21 CFR 314.95(e), Baxter Healthcare, A&CC is also submitting documentation of evidence of receipt of the subject notice in Attachment 2. This includes a copy of the US certified mail return receipt from Abbott dated January 25, 2002, and a signed copy of the acknowledgment receipt from Central Glass dated January 29, 2002, demonstrating receipt of notice on the '127 patent. To date,

neither Abbott nor Central Glass has taken action to sue Baxter Healthcare, A&CC on the '127 patent.

By way of further information, Baxter Healthcare, A&CC notes that there are two lawsuits currently pending that relate to the Baxter Healthcare, A&CC ANDA. The first lawsuit was filed on September 27, 2000 in the United States District Court for the Northern District of Illinois (Civil Action No. 00 C 5939), and relates to the '176 patent and U.S. Patent No. 6,074,668 [the '668 Patent], which patents are listed in the FDA *Orange Book* with regard to the Abbott NDA for sevoflurane (Ultane). That lawsuit followed the Baxter Healthcare, A&CC notice to Abbott on August 14, 2000, of the filing of a Paragraph IV certification for the '176 and the '668 patents.

The second lawsuit was filed on March 16, 2001 in the United States District Court for the Northern District of Illinois (Civil Action No. 01 C 1867), and relates to the '176 patent. That lawsuit followed the Baxter Healthcare, A&CC notice to Abbott on January 31, 2001, of the filing of a Paragraph IV certification for the '176 and '668 patents that related to an Amendment to the pending Baxter Healthcare, A&CC ANDA. Baxter has submitted the required notification to the FDA of the filing of these lawsuits by the patent holders.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Attachments 1, 2

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

January 22, 2002

Via Facsimile and Airborne Overnight Express

NC

NEW CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

NAI
P.M.D
1/30/02

Attention: Mr. Gary J. Buehler, Director
Office of Generic Drugs (HFD-600)

re: **ANDA 75-895 - Sevoflurane: Liquid for Inhalation**
Correspondence to Pending ANDA:
Paragraph IV Certification for U.S. Patent 6,228,127

Dear Mr. Buehler:

Reference is made to the Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] pending ANDA for sevoflurane, submitted on June 6, 2000, using Ultane®, NDA 20-478, as the reference listed drug. On January 16, 2002, the electronic version of the *Orange Book* added patent 6,288,127 (copy of the *Orange Book* listing and the patent are enclosed), issue date September 11, 2001, expiration date July 27, 2017, to the Ultane® NDA.

Enclosed please find a Paragraph IV Certification for the subject patent, 6,288,127, from Baxter Healthcare, A&CC.

If you have any questions regarding the above, please contact me, by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

CENTER FOR DRUG
JAN 23 2002
EVALUATION AND RESEARCH

enc: Form FDA 356h

NAI
gm 2/11/02

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

N/FA

January 9, 2002

***Via* Fax and Airborne Overnight Express**

ORIG AMENDMENT

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Dr. Rashmikant Patel, Director, OGD Division of Chemistry I

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: CMC (Response to telecon of 1/9/02)

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000, and amended on January 26, April 12, May 3, October 2, and October 31, 2001. Reference is also made to the Agency's telephone call of January 9, 2002 between Dr. Rashmikant Patel and Baxter Healthcare, A&CC. During the telecon, Dr. Patel requested Baxter Healthcare, A&CC to confirm that the release and stability specifications for —— content in the finished product packaged in the aluminum bottles are established at Not More Than (NMT) —— Please note that packaging for sevoflurane in the alternative — bottles was withdrawn due to business reasons on October 2, 2001.

As stated in the finished product regulatory specification, RS FP 44D, Sevoflurane Drug Product (Aluminum Bottle), [Ref: page 0297 of the January 26, 2001 Minor Amendment (which included information on the 250 mL aluminum bottles)], the stability testing protocol [Ref: page 0303 of the same amendment], and page 6 (response to comment 3) in the October 31, 2001 2nd minor amendment, Baxter Healthcare, A&CC confirms that the specifications for the allowable —— content in the sevoflurane finished product at product release and shelf life (stability) testing are established at NMT ————

A copy of the specification, RS FP 44D, and the Sevoflurane Marketed Product Stability Testing Protocol, are resubmitted for your convenience.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 10 2002
OGD

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Resubmitted Specification and Stability Testing Protocol

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

ORIG AMENDMENT
N/FA

October 31, 2001

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

re: **ANDA 75-895: Sevoflurane – Liquid for Inhalation**
Fax Amendment: ***CMC (Response to FDA letter of 10/4/01);***
Labeling (Response to FDA letter of 10/17/01

Dear Mr. Buehler:

Reference is made to the above-mentioned ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000, and amendments of April 12, May 3, and October 2, 2001. Reference is also made to the Agency's faxed deficiency letters of October 4 (Chemistry) and October 17, 2001 (Labeling), copies of which are enclosed.

This correspondence includes full responses to the above-mentioned fax deficiency letters of October 4 and 17, 2001. The responses to the Agency comments are addressed on an item-by-item basis. The responses to the Labeling comments and actual copies of the draft package insert labeling, code #460-220-05, follow the responses to the CMC comments.

This one-volume submission includes:

Responses to the FDA letter dated October 4, 2001 containing Chemistry, Manufacturing and Controls comments (pages 0001 - 0074)

Responses to the FDA letter dated October 17, 2001 containing Labeling comments (pages 0075 - 0123)

The Field Copy of the CMC responses (without the Labeling responses), as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

A signed form FDA 356h and a Table of Contents immediately follow this letter.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Attachments 1 - 13

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

VIA FACSIMILE and VIA OVERNIGHT MAIL

October 2, 2001

ORIG AMENDMENT
N/FA

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Desk Copy: Jean Min, Project Manager

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Re: **ANDA 75-895; Sevoflurane Liquid for Inhalation**

General Correspondence to the pending ANDA
Withdrawal of the 250-cc —— containers from the ANDA submitted on June 5, 2000

Dear Mr. Buehlar:

Reference is made to the aforementioned Abbreviated New Drug Application (ANDA) submitted on June 5, 2000 by Baxter Healthcare Corporation, Anesthesia & Critical Care (BHC, A&CC), (previously known as Baxter Pharmaceutical Products Inc.). This ANDA provides packaging of the product in two alternate 250 cc containers, —— and aluminum. At this time, for business reasons, according to 21 CFR 314.65, we are withdrawing ***only*** the portion of the ANDA that relates to the 250 cc —— containers including any information that specifically refers to the filling, labeling, packaging, storage and marketing of the sevoflurane liquid for inhalation in 250 cc —— containers. BHC, A&CC understands that such withdrawal is without the prejudice to re-filing of —— containers. Please note that BHC, A&CC continues to seek approval for sevoflurane packaged in 250-cc aluminum container submitted under the subject AN[illegible] on January 26, 2001.

This change is reflected in the package insert. BHC, A&CC has further revised the package insert labeling submitted on May 3, 2001 to remove the reference to the availability of sevoflurane in the ——bottles. As can be seen from the electronic

comparison of the enclosed package insert (code 460-220-04) with the one submitted in the May 3, 2001 submission (code 460-220-03), there are no other revisions made to the package insert. Four copies of the revised draft package insert (code 460-220-04) are enclosed in the archival copy.

BHC, A&CC requests that the withdrawn portion of the ANDA be kept confidential and not be released under the Freedom of Information Act (FOIA) as the full ANDA is still under the Agency review for marketing authorization.

BHC, A&CC apologizes for any inconvenience to the Agency that may have been caused by this withdrawal action. Should you need any additional information or have any questions, please do not hesitate to contact me by telephone at 908-286-7215 or by fax at 908-286-7269.

Sincerely,

Pjambhekar

Priya Jambhekar
Director, Regulatory Affairs

Enclosures: Form FDA 356h

Submitted in duplicate.

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

NAI gm 6/11/01

Baxter

June 1, 2001

Via **Airborne Express** (overnight delivery)

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

NEW CORRESP
NC

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

re: **ANDA 75-895: Sevoflurane – Liquid for Inhalation**

New Correspondence: ***Name Change of Application Holder to Baxter Healthcare Corporation***

Dear Mr. Buehler:

Reference is made to the above-mentioned ANDA for sevoflurane (ANDA 75-895) dated June 5, 2000, submitted by Baxter Pharmaceutical Products Inc. [Baxter PPI], a wholly owned subsidiary of Baxter Healthcare Corporation [BHC]. On December 31, 2000, Baxter PPI merged with BHC and its business and assets were assumed by BHC.

There is no change in the location of the company or personnel. Correspondence concerning the ANDA should continue to be addressed as follows:

Priya Jambhekar
Director, Regulatory Affairs
Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence NJ 07974

Please note that this merger has no impact on the product labeling submitted on 4/12/01 and 5/3/01 as the labeling indicates BHC to be the manufacturer and distributor of the product.

JUN 04 2001
OGD
EVALUATION AND RESEARCH

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

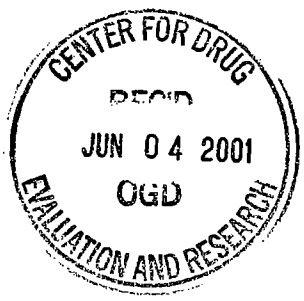
Sincerely,

PJambhekar

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h

APPEARS THIS WAY
ON ORIGINAL



Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

April 12, 2001

Via **DC Express** (same day delivery)

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Label
ORIG AMENDMENT
AM

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

re: **ANDA 75-895: Sevoflurane – Liquid for Inhalation**

Minor Amendment - Complete Responses to FDA Letters of 3/29/01 (CMC) and 2/7/01 (Labeling)

Dear Mr. Buehler:

Reference is made to the above-mentioned ANDA for sevoflurane (ANDA 75-895) dated June 5, 2000, and to the Baxter Pharmaceutical Products Inc. [Baxter PPI] Amendment dated January 29, 2001. Reference is also made to the Agency comment letters (copies enclosed) dated March 29, 2001 (CMC), and February 7, 2001 (Labeling). Reference is also made to the teleconference of April 3, 2001 between OGD and Baxter PPI to obtain clarification of the FDA comments in the March 29th letter. The Baxter PPI summary of this teleconference are included following the FDA copy-letters.

The CMC section addresses the comments on an item-by-item basis and precedes the Labeling section. The Labeling section contains final printed labeling for the — bottle (code 460-217-01), the Aluminum bottle (code 460-263-00), and the ——— (code 460-218-01), as well as the *draft* package insert (code 460-220-02), revised to incorporate the Agency's comments.

For your information, also enclosed are copies of the Baxter Healthcare notifications of revised Paragraph 4 certification to Abbott and ———, and their receipt acknowledgments.

The Field Copy (volume 1, without the Labeling response), as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

NW April 18, 01

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 13 2001
OGD

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division

Regulatory Affairs
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

October 11, 2000

NEW CORRESP
NC

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855

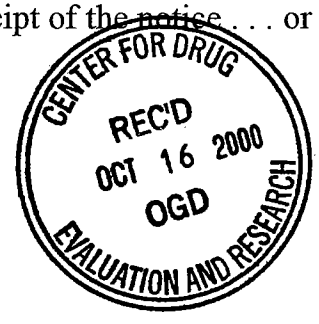
ATTENTION: Gary Buehler
Acting Director

RE: Abbott Laboratories v. Baxter Pharmaceutical Products, Inc. et al.
Sevoflurane ANDA 75-895

ANDA 75-895 filed by Baxter Pharmaceutical Products, Inc. ("Baxter") contains certifications under 21 U.S.C. §355(j)(2)(A)(vii)(IV) asserting that the manufacture, use and sale of its Sevoflurane Liquid for Inhalation in a — bottle, does not infringe any United States patent owned by Abbott Laboratories and/or —— Specifically, the certification is to U.S. Patent Nos. 6,704,668 and 5,990,176. Notice of these certifications were received by Abbott on August 15, 2000 and shortly thereafter by —— (with respect to U.S. Patent No. ——

This letter is to advise the FDA that on September 27, 2000, Abbott filed a lawsuit against Baxter in federal district court in Chicago, Illinois, alleging infringement of the '668 patent and '176 patents. A copy of the lawsuit is enclosed. (No. 00 C 5939 (N.D. Ill., filed September 27, 2000).)

Because Abbott has filed its action within 45 days of receipt of notice of the certification, pursuant to the Federal Food, Drug and Cosmetic Act, §505(j)(4)(B)(iii), the agency cannot approve ANDA 75-895 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice . . . or such shorter or longer period as the court may order . . ."



Should you have any questions concerning this matter, please feel free to contact me directly.

Very truly yours,

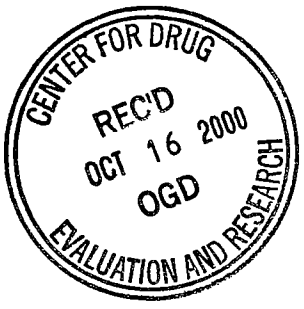
Nancy Conway
Director, Regulatory Affairs
(847) 935-0595
Fax (847) 938-7867
Office of Generic Drugs

ccs: Cecelia Parise, Special Assistant
Peter Rickman Acting Director, Division of Labeling and Program Support
Donald Hare, Special Assistant

Mary Ann Holovac
Information Services Team

Location address:
(for FedX deliveries)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93 Room #3012
12420 Parklawn Drive
Rockville, MD 20857-0001

Mailing address: (US Mail)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane Rockville, MD 20857



Regulatory Affairs

Baxter Pharmaceutical Products Inc. 908.286.7000
95 Spring Street
New Providence, New Jersey 07974

Baxter

October 10, 2000

Via *Airborne overnight Express*

NEW CORRESP
NC

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

Attention: Mr. Gary J. Buehler, Acting Director
Office of Generic Drugs (HFD-600)

Desk copy: Mr. Gregg Davis, Regulatory Management Officer

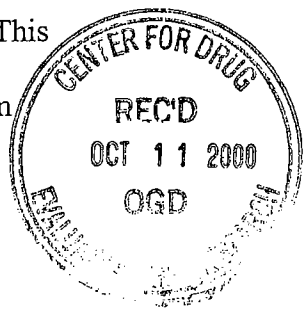
re: **ANDA 75-895**
Sevoflurane: Liquid for Inhalation
Correspondence to Pending ANDA

Dear Mr. Buehler:

Reference is made to the aforementioned ANDA, submitted by Baxter Pharmaceutical Products Inc. [Baxter PPI] on June 5, 2000 and accepted for filing on August 3, 2000, which included a paragraph 4 certification against Patents 5,990,176 ('176 patent) and 6,074,668 ('668 patent). The '176 patent lists Abbott Laboratories (Abbott) and Central Glass Co. Limited (Central Glass) as the patent holders, and the '668 patent lists Abbott as the patent holder.

As required under 21 CFR 314.95 (b), on August 14, 2000, the law firm of Sidley and Austin notified *via* US certified return receipt requested mail to Abbott, on behalf of Baxter PPI, of the filing of an ANDA for sevoflurane with paragraph 4 certifications for '176 and '668 patents, and to Central Glass for the '176 patent. A follow-up letter was sent to Central Glass on September 14, 2000. Copies of the notification letters are enclosed as Attachment 1

According to 21 CFR 314.95(e), Baxter PPI is also submitting documentation of notification of receipt of the subject notice in Attachment 2. This includes a copy of the US certified mail return receipt from Abbott dated August 15, 2000, demonstrating receipt of notice on '176 and '668 patents. Please note that Central Glass did not return the certified mail receipt in response to the original request of August 14 or the follow-up of September 14. However, Baxter PPI has other evidence to demonstrate receipt of notice by Central Glass on the '176 patent. This evidence comes from the lawsuit filed by Abbott and Central Glass. Page 3, paragraph 2 of this suit states that Central Glass received the subject notice from Baxter PPI on or about August 18, 2000. A copy of this page is enclosed.



In accordance to 21 CFR 314.107(f)(2), Baxter PPI hereby certifies that a lawsuit was filed by the patent holders(s) within 45 days from the date of notification. This lawsuit was filed in the United States District Court Northern District of Illinois on September 27, 2000 (docket number 00C 5939). A copy of the lawsuit is included as Attachment 3.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

75-895

SIDLEY & AUSTIN
A PARTNERSHIP INCLUDING PROFESSIONAL CORPORATIONS

DALLAS
LOS ANGELES
NEW YORK
WASHINGTON, D.C.

BANK ONE PLAZA
10 S. DEARBORN STREET
CHICAGO, ILLINOIS 60603
TELEPHONE 312 853 7000
FACSIMILE 312 853 7036

HONG KONG
LONDON
SHANGHAI
SINGAPORE
TOKYO

FOUNDED 1866

WRITER'S DIRECT NUMBER
(312) 853-7017

WRITER'S E-MAIL ADDRESS
habrams@sidley.com

NAI
9/11/00

August 25, 2000

NEW CORRESP

NC

As this letter was addressed & sent to DISB, no further action is indicated at this time

Gregory D. Ibe
9/11/00

VIA FEDERAL EXPRESS

Drug Information Services Branch (HFD-84)
Center for Drug Evaluation & Research
Food & Drug Administration
Room 3012
12420 Parklawn Drive
Rockville, MD 20857-0001

RE: Sevoflurane – Liquid for Inhalation: Request for De-Listing of U.S. Patent No. 5,990,176 and U.S. Patent No. 6,074,668 from *Approved Drug Products With Therapeutic Equivalence Evaluations* Register, Pursuant to 21 C.F.R. § 314.53(f)

Dear Sir or Madam:

We represent Baxter Pharmaceuticals Products, Inc. ("Baxter"). On June 6, 2000, Baxter submitted to the United States Food & Drug Administration ("FDA") an Abbreviated New Drug Application ("Application") under 21 U.S.C. § 355(j)(1) and (2)(A), to obtain approval to engage in the commercial manufacture, use, and sale of Sevoflurane - Liquid for Inhalation. In the Application, Baxter indicated that it intends to market a generic sevoflurane drug product, which went off-patent eleven years ago, before the expiration of U.S. Patent No. 5,990,176 (hereinafter, "the '176 patent"). The Application includes a 21 U.S.C. § 355(j)(2)(A)(vii)(IV) certification that, in Baxter's opinion and to the best of its knowledge, the '176 patent is invalid and/or not infringed.

On July 10, 2000, Baxter amended its Application to advise the FDA that Baxter intends to market its generic sevoflurane drug product before the expiration of a second, new patent U.S. Patent No. 6,074,668 (hereinafter, "the '668 container patent"). The amended Application includes a 21 U.S.C. § 355(j)(2)(A)(vii)(IV) certification that, in Baxter's opinion and to the best of its knowledge, the '668 container patent is invalid and/or not infringed.

Baxter filed the certifications with respect to the '176 patent and the '668 container patent solely because Abbott listed these patents in FDA's *Approved Drug Products wi*

Therapeutic Equivalence Evaluations register (commonly known and referred to hereinafter as "the Orange Book"). However, Baxter believes that Abbott has improperly listed the '176 patent and the '668 container patent in the Orange Book, and that Baxter should not have been put to the task of having to provide these certifications. Nor should Baxter be put to the risk of delays in the final approval of its Application or the costs of meritless patent litigation because of Abbott's improper listing of these patents in the Orange Book. Therefore, Baxter is requesting that FDA promptly remove the '176 patent and the '668 container patent from the Orange Book in accordance with 21 C.F.R. § 314.53(f).

Baxter relied for its Application on NDA 20-478, which was approved June 7, 1995. We further understand that the "drug" for which Abbott submitted the application was sevoflurane, without any other active or inactive ingredients. Hence, the only patent claiming "the drug" that could properly have been listed would have been a patent claiming sevoflurane alone. However, the patent claiming sevoflurane alone – U.S. Patent No. 3,689,571 ("the '571 patent") – expired eleven years ago.

The relevant statute, 21 U.S.C. § 355(c)(2), requires that the holder of an approved application, in this case Abbott, shall list the patent number and expiration date of any patent which (1) claims *the drug* for which the applicant submitted the application (or claims a method of using *the drug*) and (2) "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of *the drug*" (emphasis supplied).

Unlike the expired '571 patent, the '176 and '668 patents do not claim *the drug* "sevoflurane." *See General Foods Corp. v. Studiengesellschaft Kohle mbh*, 972 F.2d 1272, 1274 (Fed. Cir. 1992) ("It cannot be said – though it often is, incorrectly, by the uninitiated, that a part of a claim is 'claimed' subject matter"). The only composition "claimed" in the '176 patent is an anesthetic composition that includes the combination of sevoflurane with a Lewis acid inhibitor; i.e., sevoflurane and the inhibitor in a container environment where there are Lewis acids that need to be inhibited. By the same token, the only products "claimed" in the '668 container patent are *containers* constructed (either in part or in whole) from polyethylene napthalate ("PEN"), which include a certain volume of sevoflurane. As such, the '176 and '668 patents do not satisfy either prong of the relevant statute.

We also note that the pertinent NDA was approved at least eighteen months before the original application for the '176 patent and at least two and a half years before the original application for the '668 patent. If the composition and product claimed in the '176 and '668 patents are regarded as "the drug," these products were allegedly not even invented at the time of the pertinent NDA. Hence the NDA cannot justify or support the listing.

In conclusion, Baxter believes that Abbott has improperly listed the '176 patent and the '668 container patent in the Orange Book, such that Baxter should not have been put to the burden of preparing and filing certifications with respect to these patents. Nor should

Baxter's Application for the generic drug product sevoflurane, which went off-patent eleven years before Abbott's improper listings of the '176 patent and the '668 container patent, be delayed by Abbott's abuse of the patent listing requirements. Consequently, Baxter respectfully requests that FDA promptly contact Abbott pursuant to 21 C.F.R. § 314.53(f) and request that Abbott remove the '176 patent and the '668 container patent its NDA. If Abbott fails to do so, FDA should take enforcement action against Abbott for submitting a false statement to the agency and remove the subject patent from the Orange Book.

Very truly yours,

Hugh A. Abrams

Hugh A. Abrams

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

June 5, 2000

***Via* Hand Delivery**

Paragraph 4 Patent Certification Enclosed

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

re: **Original ANDA – Sevoflurane – Liquid for Inhalation**

Dear Mr. Buehler:

According to 21 CFR 314.94, Baxter Pharmaceutical Products Inc. [Baxter PPI] is submitting in duplicate an ANDA for Sevoflurane. The Reference Listed Drug (RLD) used is Ultane® (sevoflurane), NDA 20-478, approval date June 7, 1995. The Baxter PPI sevoflurane contains same strength, dosage form and route of administration as Ultane. The only difference is in the type of container closure system used. Ultane is packaged in 250-mL amber glass bottles and Baxter PPI generic sevoflurane product is packaged in [redacted] bottle.

In accordance with Waxman-Hatch Act, at the time of approval of Ultane NDA, it was awarded a 5-year market exclusivity, which is reserved for approval of a new chemical entity. According to the FDA Orange Book, this exclusivity expires on June 7, 2000. However, as reflected in the December 23, 1999 version of the Orange Book, the Ultane NDA recently added a composition patent, number 5, 990, 176 (issued November 23, 1999, expiration date, January 27, 2017).

Waxman-Hatch Act allows an applicant to submit an ANDA after four (4) out of five (5) years of market exclusivity has been passed, if the applicant is submitting an ANDA containing paragraph IV certification. This provision makes ANDA filing for sevoflurane using Ultane as a RLD eligible after June 7, 1999. Accordingly, Baxter PPI is submitting an abbreviated new drug application for marketing of generic sevoflurane before expiration of its five-year market exclusivity on June 7, 2000.

Based upon the telecommunications with the Agency, Baxter PPI understands that no other ANDA has been accepted for filing for marketing approval of generic sevoflurane using

Ultane as RLD as of this date. Assuming that is the case as of this filing, Baxter PPI trusts that Baxter PPI sevoflurane ANDA will be the first ANDA filed containing a paragraph IV certification and will become eligible to receive six (6) months of exclusive market exclusivity.

This submission is formatted in accordance with "Guidance for Industry: Organization of an Abbreviated New Drug Application and Abbreviated Antibiotic Application" (FDA/CDER, April 1997), and the ANDA sections are organized as follows:

ANDA Sections	Submission Volume
Cover Letter, Debarment Certification, Field Copy Documentation, Table of Contents.	1
1 – 7	1
8.1.1 – 8.1.4	2
8.1.5 – 8.6	3
9 – 14	4
15 – 21	5
6 *Bio-equivalence review copy*	6
16 *Two extra sets of MVP*	7, 8

The archival copy is submitted in blue jackets, the Chemistry, Manufacturing, and Controls review copy (without Section 5 – Labeling) is bound in red, and the Bio-equivalence review copy (volume 6) is in an orange jacket. Two extra sets of the Methods Validation Package, volumes 7 and 8, are also included.

The Field Copy (volumes 1 through 5, without Section 5 - Labeling), as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Baxter PPI will initiate the due process of notification to the RLD application holder and patent holder(s) of filing the subject ANDA with paragraph IV certification upon receiving a notification from the Agency of acceptability of this ANDA for filing. Also, please note that, although the composition patent was added to the RLD NDA just recently, it is not clear from the review of the Orange Book whether there ever was a supplemental NDA filed and approved for a change in the formulation of the RLD and as a result whether the previous formulation was withdrawn from the NDA. Due to this reason, under a separate cover, Baxter PPI is submitting a citizen petition to allow for filing of this ANDA, although we do not believe that such petition is required. Should you have any questions,

please do not hesitate to contact me by telephone at 908/286-7215 or by facsimile at 908/286-7269.

Sincerely,

David Zering for PJ

Priya Jambhekar
Director, Regulatory Affairs

enc: Original ANDA

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

July 28, 2000

via Airborne Express

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

NEW CORRESP
NC

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

Desk copy: Mr. Greg Davis, OGD Project Manager

re: **ANDA 75-895: Sevoflurane – Liquid for Inhalation**

Dear Mr. Buehler:

Reference is made to the Baxter Pharmaceutical Products Inc. [Baxter PPI] pending ANDA for sevoflurane, original application dated June 5, 2000. Reference is also made to a telephone call from Greg Davis, OGD Project Manager, on July 27, 2000, in which the *original signed* cGMP certification (page 0841 of the ANDA) was requested.

The original cGMP certification from the Baxter Caribe manufacturing facility is enclosed. It would be much appreciated if you would now replace page 0841 of the ANDA with this *orignal* cGMP certification.

We apologize for any inconvenience caused. Please contact me at 908/286-7215, or fax me at 908/286-7269 if you have any questions. With many thanks!

Sincerely,

David Zuring for

Priya Jambhekar
Director, Regulatory Affairs

enc: Original cGMP Certification, page 0841 of original ANDA

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

July 10, 2000

Via Facsimile *and Airborne overnight Express mail*

NEW CONS...

Food and Drug Administration
Center for Drug Evaluation and Research
Department of Health and Human Services
7500 Standish Place, Room 286
Rockville MD 20857

N 75895

Attention: Mr. Gary J. Buehler, Acting Director
Office of Generic Drugs (HFD-600)

re: **Sevoflurane: Liquid for Inhalation**
Correspondence to Pending ANDA

Dear Mr. Buehler:

Reference is made to the Baxter Pharmaceutical Products Inc. [Baxter PPI] pending ANDA for sevoflurane, submitted on June 6, 2000. At the time of the ANDA filing, the *Orange Book* listed only patent 5,990,176 against the Ultane® NDA, #20-478.

Subsequent to the filing of this ANDA, on June 21, 2000, the electronic version of the *Orange Book* added patent 6,074,668, issue date June 13, 2000, expiration date January 9, 2018, to the Ultane® NDA.

Accordingly, Baxter PPI is submitting a Paragraph 4 patent certification against Abbott patent 6,074,668.

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office. Also enclosed is a Field Copy Certification Statement.

If you have any questions regarding the above, please contact me, by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

PJambhekar

Priya Jambhekar
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 11 2000
OGD

enc: Form FDA 356h

ANDA 75-895

Baxter Pharmaceutical Products Inc.
Attention: Priya Jambhekar
95 Spring Street
New Providence, NJ 07974

AUG 3 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated July 26, 2000 and your correspondence dated July 28, 2000.

NAME OF DRUG: Sevoflurane Inhalation Liquid, 100%, 250 mL bottles

DATE OF APPLICATION: June 5, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 6, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter

immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301)827-5862.

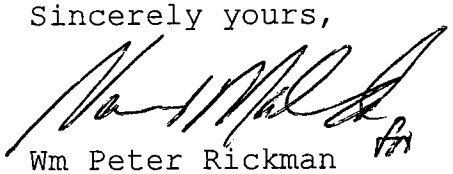
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Regulatory Affairs

Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, New Jersey 07974

908.286.7000

Baxter

January 26, 2001

***Via* Airborne overnight Express**

Revised Paragraph 4 Patent Certification Enclosed

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

NDA ORIG AMENDMENT

Attention: Mr. Gary Buehler
Acting Director, Office of Generic Drugs [OGD]

re: **ANDA 75-895: Sevoflurane – Liquid for Inhalation**
Minor Amendment - Response to FDA Letter of 11/27/00

Dear Mr. Buehler:

Reference is made to the Agency's letter dated November 27, 2000 (copy attached) which contained CMC and Labeling comments on the above-cited pending ANDA submitted June 5, 2000. Baxter Pharmaceutical Products Inc. [Baxter PPI] is submitting herewith a complete response to the questions raised in the said "minor deficiency" letter.

Responses to the CMC comments (including information for 250 mL aluminum bottles) precedes the Labeling section. The Labeling section contains final printed labeling, which was revised to include the Agency's comments on the container labels and the package insert.

The Field Copy (volume 1, without the Labeling response), as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215 or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 30 2001
OGD

enc: Form FDA 356h

2/1/01

Priya Jambhekar
Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence NJ 07974
tel: 908/286-7215 *fax*: 908/286-7269

Baxter

To: **Mr. Gary Buehler** **Fax #: 301/594-0183**

At: **FDA - OGD (HFD-600)**

Pages: 11 (including cover) **Date: 4/8/02**

☑ URGENT ☑ For Review ☐ As requested ☐ Please Comment ☐ Please Reply

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- **Subject: ANDA 75-895: Sevoflurane, Liquid for Inhalation**
  Telephone Amendment – CMC (Response to telecon of 4/8/02)

Dear Mr. Buehler,

The following pages contain copy of the above Telephone Amendment, hard copy of which is being sent *via* Airborne overnight Express.

If you have any questions, please call me at 908/286-7215 or fax me at 908/286-7269.

Priya Jambhekar
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

April 8, 2002

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Dr. Andrew Langowski, Chemist, OGD Division of Chemistry I

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: CMC (Response to telecon of 4/8/02)

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000. Reference is also made to the minor amendment submitted on January 26, 2001.

Pursuant to a telephone request today from Dr. Andrew Langowski, Baxter Healthcare, A&CC, is resubmitting a copy of the sevoflurane drug substance specification, RS API 32D, which was originally submitted to this ANDA on January 26, 2001 (page 180).

The Field Copy, as per 21 CFR 314.96(b), is being submitted concurrently to the North Brunswick Resident Inspection Post of the Newark District Office.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Resubmitted Specification and Stability Testing Protocol

Medication Delivery

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974
908.286.7000

Baxter

April 8, 2002

Ms. Regina Brown
Pre-Approval Manager
Food and Drug Administration
Hovnanian Community Center
120 North Center Drive (Building C)
North Brunswick NJ 08902

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment - Response to FDA telecon of 4/8/02

Dear Ms. Brown:

Baxter Healthcare Corporation, Anesthesia & Critical Care. is providing you with the field copy of a ***Telephone Amendment*** to the pending ANDA for Sevoflurane, submitted concurrently to the FDA Office of Generic Drugs.

As per 21 CFR 314.94(d)(5), the field copy consists of the following:

1. copies of the cover letter and application form FDA 356h;
2. certification that the field copy is a true copy of the ***Telephone Amendment*** submitted to the FDA Office of Generic Drugs;

If you have any questions or comments regarding this submission, please contact me at 908/286-7102.

Sincerely,

David L. Rohrbach
Vice President, Division Quality

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

July 2, 2002

***Via* Fax and Airborne Overnight Express**

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Jeen Min, OGD Project Manager
Dr. Glen J. Smith, Chemistry Division, OGD

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: (Response to telecon of 7/2/02)

Dear Mr. Buehler:

Reference is made to the above-mentioned pending ANDA for sevoflurane (ANDA 75-895) submitted by Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC] on June 5, 2000.

Reference is also made to the telephone conference of July 2, 2002, between Dr. Glen Smith, OGD Chemistry Team Leader, Team 9, and Baxter Healthcare, A&CC. As discussed, Baxter Healthcare, A&CC acknowledges that the method validation reports from the FDA Analytical Laboratories are still awaited, and makes a commitment to fully co-operate with FDA to resolve any issues related to validation of the analytical test methods.

Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Pjambhekar

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h

Regulatory Affairs

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Tel: 908.286.7000
Fax: 908.286.7269

Baxter

Via DC Express

June 28, 2002

ANDA filed with Paragraph 4 Certification

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room - MPN-2
7500 Standish Place, Room 150
Rockville MD 20855-2773

ORIG AMENDMENT
N/AF

Attention: Mr. Gary Buehler
Director, Office of Generic Drugs [OGD]

Desk Copies: Mr. Robert West, OGD Deputy Director
Mr. Jeen Min, OGD Project Manager
Mr. Chan Park, OGD - Division of Labeling

re: **ANDA 75-895, Sevoflurane – Liquid for Inhalation**
Telephone Amendment: Submission of Revised Final Printed Package Insert Labeling

Dear Mr. Buehler:

Reference is made to the above-referenced pending ANDA for Sevoflurane – Liquid for Inhalation, submitted on June 5, 2000. Reference is also made to the teleconference of June 25, 2002 between Mr. Chan Park, Division of Labeling, OGD, and Baxter Healthcare Corporation, Anesthesia & Critical Care [Baxter Healthcare, A&CC], and to the confirmatory eMail from Mr. Park (copy enclosed). As requested by Mr. Park, Baxter Healthcare, A&CC has revised the final printed package insert to replace the name "Ultane" in the 2nd paragraph of the CLINICAL PHARMACOLOGY (Clinical Trials, Pediatric Anesthesia) subsection with "Sevoflurane" as follows:

> "... is approved for Abbott Laboratories' Sevoflurane."

In addition, according to Mr. Park's request, the disclaimer for Ultane in the HOW SUPPLIED section has been deleted, and the revision date changed to "June 2002". There are no other revisions. Copies of the package insert, annotated to show the above revisions, are enclosed.

Baxter Healthcare, A&CC, herewith submits fourteen [14] sets of revised final printed package insert labeling, incorporating the requested revisions, as follows: twelve [12] sets in the Archival copy, and two [2] sets in the Review copy.

RECEIVED
JUN 2 8 2002
OGD / CDER

Baxter Healthcare, A&CC believes this submission completes all requirements for final approval of this product. Should you have any questions, please do not hesitate to contact me by telephone at 908/286-7215, or by facsimile at 908/286-7269.

Sincerely,

Priya Jambhekar
Director, Regulatory Affairs

enc: Form FDA 356h
Final Printed Package Insert, code 460-220-07, rev. 6-02

APPEARS THIS WAY
ON ORIGINAL