* Anesthesia Machine Kit enclosed:
1. Isoflurane
2. Ultane Sevoflurane

MATERIAL SAFETY DATA SHEET

Product Name: Isoflurane, USP

1. CHEMICAL PRODUCT AND COMPANY INFORMATION

12630

Manufacturer Name And Address	Hospira, Inc. 275 North Field Drive Lake Forest, Illinois 60045 USA
Note:	Hospira, formerly the Hospital Products Division of Abbott Laboratories, was created as an independent company in May 2004.
Emergency Telephone Hospira, Inc.	CHEMTREC: 800 424-9300 224 212-2055
Product Name	Isoflurane, USP
Synonyms	None

2. COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient Name	Isoflurane
Chemical Formula	$C_3H_2ClF_5O$

Component	Approximate Percent by Weight	CAS Number	RTECS Number
Isoflurane	100	26675-46-2	KN6799000

3. HAZARD INFORMATION

Emergency Overview	In clinical use, this material is used to produce anesthesia (sleep). Large concentrations are required to produce this effect. Smaller amounts could produce drowsiness. Possible target organs include the central nervous system, cardiovascular system, and respiratory system.
Occupational Exposure Potential	Information on the absorption of this compound via ingestion, inhalation or skin contact is not available. Avoid liquid aerosol generation and skin contact.
Signs and Symptoms	No signs or symptoms from occupational exposure are known. Clinical data suggest the following: headaches, incoordination, nausea, slow hart rate, sedation sleep, drowsiness, dizziness, hyperthermia, vomiting, breathing difficulty.
Medical Conditions Aggravated by Exposure	Hypersensitivity to the material and/or similar materials. Pre-existing ailments in the following organs: central nervous system, cardiovascular system, gastrointestinal system, respiratory system.

4. FIRST AID MEASURES

Eye Contact: Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Skin Contact: Remove from source of exposure. Flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. Provide symptomatic/supportive care as necessary.

Inhalation: Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic / supportive care as necessary.

Ingestion: Remove from source of exposure. If signs of toxicity occur, seek medical attention. Provide symptomatic / supportive care as necessary.

5. FIRE FIGHTING MEASURES

Flammability: Non-flammable.

Fire & Explosion Hazard: None

Extinguishing Media: Use extinguishing media appropriate for primary cause of fire.

Special Fire Fighting Procedures No special provisions required beyond normal fire fighting equipment such as flame and chemical resistant clothing and self contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Spill Cleanup and Disposal Absorb liquid with suitable material and clean affected area with soap and water. Dispose of materials according to the applicable federal, state, or local regulations.

7. HANDLING AND STORAGE

Handling Avoid contact with eyes, skin, or clothing. Wash thoroughly after handling. Do not eat, drink or smoke near material.

Storage No special storage required for hazard control. For product protection store at controlled room temperature of 15-30°C (59-86°F).

Special Precautions Protect from freezing and extreme heat.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Guidelines

	Exposure limits		
Component	**OSHA-PEL**	**ACGIH-TLV**	**Hospira EEL**
Isoflurane	8 hr TWA: Not Established	8 hr TWA: Not Established	8 hr TWA: 450 mg/m3 (60 ppm) STEL: Not Established

Notes: OSHA PEL: US Occupational Safety and Health Administration – Permissible Exposure Limit
ACGIH TLV: American Conference of Governmental Industrial Hygienists – Threshold Limit Value.
EEL: Employee Exposure Limit.
TWA: 8 hour Time Weighted Average.
STEL: 15-minute Short Term Exposure Limit.

Respiratory Protection	Respiratory protection is not needed during normal product use.
Skin Protection	If solution contact with unprotected skin is likely, use of impervious gloves is a prudent practice.
Eye Protection	Eye protection is not required during expected product use conditions but may be warranted should a splash potential exist.
Engineering Controls	Engineering controls are not needed during normal product use conditions. Anesthetic gas scavenging systems should be used to control waste anesthetic. In the laboratory, this product should be handled in a hood.

9. PHYSICAL/CHEMICAL PROPERTIES

Appearance/Physical State	Clear, colorless liquid.
Odor	Mild, pungent, musty, ethereal odor
Boiling Point	48.5 °C at 760 mm Hg
Freezing Point	Approximately that of water (0 °C, 32 °F).
Vapor Pressure	295 mm Hg at 25 °C
Vapor Density (Air=1)	6.3
Evaporation Rate	Not Applicable
Bulk Density	Not Determined
Specific Gravity	1.496 at 25 °C
Solubility	Slightly soluble in water
pH	Not Applicable

10. STABILITY AND REACTIVITY

Chemical Stability	Stable under standard use and storage conditions.
Incompatibilities	Not Determined
Hazardous Decomposition Products	Toxic fumes of chlorine and fluorine under fire conditions
Hazardous Polymerization	Not Determined.

11. TOXICOLOGICAL INFORMATION:

Acute Toxicity:

Ingredient(s)	Percent	Test Type	Value	Units	Species
Isoflurane	100	LD50	4770-5080	mg/kg	Mice
		LC50	15,300-16,800		Rats

LC50 is the concentration in air that produces 50% mortality.

Mutagenicity	Not Determined
Target Organ Effects	In clinical use target organ effects include the central nervous system.

12. ECOLOGICAL INFORMATION:

Aquatic Toxicity	Not Available

13. DISPOSAL CONSIDERATIONS:

Waste Disposal	Disposal should be performed in accordance with the federal, state or local regulatory requirements.
Container Handling and Disposal	Dispose of container and unused contents in accordance with federal, state, and local regulations.

14. TRANSPORTATION INFORMATION

DOT	Not Regulated

Notes: DOT - US Department of Transportation Regulations

15. REGULATORY INFORMATION

TSCA Status	Not Regulated
CERCLA Status	Not Regulated
SARA Status	Not Regulated
RCRA Status	Not Regulated
PROP 65 (Calif.)	Not Regulated

Notes: TSCA Toxic Substance Control Act
CERCLA, US EPA law, Comprehensive Environmental Response, Compensation, and Liability Act
SARA Superfund Amendments and Reauthorization Act
RCRA US EPA, Resource Conservation and Recovery Act
Prop 65, California Proposition 65

16. OTHER INFORMATION:

MSDS Coordinator	T. Straits MPH, CIH
Date Prepared	September 15, 2005

Disclaimer:
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ABBOTT LABORATORIES -- 4456 ULTANE SEVOFLURANE

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MSDS Safety Information

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MSDS Date: 12/23/1998
MSDS Num: CLCDK
Product ID: 4456 ULTANE SEVOFLURANE
MFN: 02
Responsible Party
Cage: 33110
Name: ABBOTT LABORATORIES
Address: 100 ABBOTT PARK RD
City: ABBOTT PARK IL 60064-3500
Info Phone Number: 847-937-3386
Emergency Phone Number: 1-847-937-7970
Preparer's Name: DLF
Chemtrec IND/Phone: (800)424-9300
Review Ind: Y
Published: Y

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Contractor Summary

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Cage: 33110
Name: ABBOTT LABORATORIES INC DIAGNOSTICS DIV
Address: 100 ABBOTT PARK RD
City: NORTH CHICAGO IL 60064
Phone: 847-935-7177

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Ingredients

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Cas: 28523-86-6
RTECS #: KO0737000
Name: SEVOFLURANE
Other REC Limits: 8 HR TWA: 100 PPM

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Health Hazards Data

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Route Of Entry Inds - Inhalation: YES
Ingestion: NO
Carcinogenicity Inds - NTP: NO
IARC: NO
OSHA: NO
Effects of Exposure: THIS MATERIAL IS USED TO PRODUCE ANESTHESIA (SLEEP). TARGET ORGANS INCLUDE THE CENTRAL NERVOUS SYSTEM, RESPIRATORY SYSTEM, CARDIOVASCULAR SYSTEM & POSSIBLY THE FETUS.
Explanation Of Carcinogenicity: NONE
Signs And Symptions Of Overexposure: SEVOFLURANE PRODUCES ANESTHESIA W/SYMPTOMS OF: RESPIRATORY DEPRESSION, HYPOTENSION, BRADYCARDIA, SHIVERING, NAUSEA, HEADACHE. LARGE CONCENTRATIONS OF SEVOFLURANE HAVE PRODUCED SLIGHT ELEVATIONS IN SE RUM ENZYMES & PRODUCED MATERNAL EFFECTS, FETAL EFFECTS (DECREASED WEIGHT GAINS), CLEFT PALATE & DECREASED REPRODUCTIVE PERFORMANCE IN ANIMAL STUDIES.
Medical Cond Aggravated By Exposure: PATIENTS SENSITIVE TO HALOGENATED ANESTHETICS; CARDIOVASCULAR/RESPIRATORY DISEASES.
First Aid: EYES/SKIN/INGESTION/INHALATION: REMOVE FROM SOURCE OF EXPOSURE. FLUSH SKIN & EYES W/COPIOUS AMOUNTS OF WATER. PROVIDE SYMPTOMATIC/SUPPORTIVE CARE, MAINTAINING VENTILATION W/PURE OXYGEN AS NECESSARY.

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Handling and Disposal

Spill Release Procedures: VENTILATE AREA & WASH SITE AFTER MATERIAL WIPE UP IS COMPLETE. COLLECT AS POISONOUS ORGANIC CHEMICAL, PLACE IN CONTAINER & HOLD FOR WASTE DISPOSAL.
Waste Disposal Methods: DISPOSE OF IN ACCORDANCE W/LOCAL, STATE & FEDERAL REGULATIONS.
Handling And Storage Precautions: STORE AT CONTROLLED ROOM TEMPERATURE OF 59-86F. KEEP CONTAINERS CLOSED & AWAY FROM LIGHT.

Fire and Explosion Hazard Information

Flash Point Text: NON-FLAMMABLE
Autoignition Temp Text: N/D
Lower Limits: N/D
Upper Limits: N/D
Extinguishing Media: WATER SPRAY, CO2/DRY CHEMICAL POWDER
Fire Fighting Procedures: WEAR SELF CONTAINED BREATHING APPARATUS.
Unusual Fire/Explosion Hazard: AVOID INHALATION OF COMBUSTION PRODUCTS.

Control Measures

Respiratory Protection: IF ENGINEERING CONTROLS ARE IN PLACE, RESPIRATORS ARE GENERALLY NOT REQUIRED. ENTRY INTO AREAS OF UNKNOWN AIRBORNE CONCENTRATION OF THIS PRODUCT SHOULD ONLY BE MADE W/A SELF CONTAINED BREATHING APPARA TUS.
Ventilation: IN THE LABORATORY ENVIRONMENT, THIS PRODUCT SHOULD BE HANDLED IN A HOOD.
Protective Gloves: IMPERVIOUS
Eye Protection: UNDER NORMAL USE CONDITIONS, NO PROTECTION IS ANTICIPATED.
Work Hygienic Practices: WASH THOROUGHLY AFTER HANDLING.

Physical/Chemical Properties

Boiling Point: =58.6C, 137.5F
Vapor Pres: 245.5
Vapor Density: 6.94
Spec Gravity: 1.525
PH: 7-7.5
Evaporation Rate & Reference: HIGHLY VOLATILE
Solubility in Water: 0.01
Appearance and Odor: CLEAR, COLORLESS LIQUID

Reactivity Data

Stability Indicator: YES
Materials To Avoid: ALKALINE EARTH METALS, STRONG BASES
Hazardous Decomposition Products: CO, CO2, HYDROGEN FLUORIDE
Hazardous Polymerization Indicator: NO

Toxicological Information

Toxicological Information: ORAL: LD50=10,800-37,200 MG/KG IN MICE AND RATS. INHALATION: LC50=58,000-83,000 PPM/1H IN RATS AND MICE, 28,300-29,000 PPM/3 H IN RATS AND MICE, 33,000-45,000 PPM/3H IN 7-14 DAY OLD NEONATAL RATS AND MICE, 73,000-106,000 PPM/1H IN DOGS AND RABBITS AND 68,000 PPM/3H IN MONKEYS. OCULAR IRRITATION: SEVOFLURANE WAS SLIGHTLY IRRITATING IN AN EYE IRRITATION TEST IN RABBITS. SPECIAL TARGET ORGAN EFFECTS: CLINICALLY, SEVOFLURANE PRODUCES ANESTHESIA WITH A MINIMUM ALVEOLAR CONCENTRATION OF 20,000 PPM. A SMALL AMOUNT OF AN INSPIRED DOSE IS METABOLIZED TO FLUORIDE AND A FLUORIDE CONTAINING METABOLITE.

Ecological Information
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MSDS Transport Information
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Transport Information: IATA/ICAO STATUS: REGULATED; PROPER SHIPPING NAME: AVIATION REGULATED LIQUID, N.O.S. (SEVOFLURANE).; HAZARD CLASS: 9; UN NUMBER: UN3334
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Regulatory Information
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Other Information
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Other Information: THE INFORMATION/RECOMMENDATIONS CONTAINED HEREIN ARE BELIEVED TO BE RELIABLE. ABBOTT LABORATORIES DOES NOT GUARANTEE THEIR ACCURACY/COMPLETENESS NOR SHALL ANY OF THIS INFORMATION CONSTITUTE A WARRANTY , WHETHER EXPRESSED/IMPLIED, AS TO THE SAFETY OF THE GOODS, THE MERCHANTABILITY OF THE GOODS/THE FITNESS OF THE GOODS FOR A PARTICULAR PURPOSE. ADJUSTMENT TO CONFORM W/ACTUAL CONDITIONS OF USAGE MAY B E REQUIRED. ABBOTT LABORATORIES ASSUMES NO RESPONSIBILITY FOR RESULTS OBTAINED/FOR INCIDENTAL/CONSEQUENTIAL DAMAGES ARISING FROM THE USE OF THESE DATA.
==========
HAZCOM Label
==========
Product ID: 4456 ULTANE SEVOFLURANE
Cage: 33110
Company Name: ABBOTT LABORATORIES INC DIAGNOSTICS DIV
Street: 100 ABBOTT PARK RD
City: NORTH CHICAGO IL
Zipcode: 60064
Health Emergency Phone: 1-847-937-7970
Label Required IND: Y
Date Of Label Review: 04/19/2001
Status Code: A
Origination Code: G
Hazard And Precautions: THIS MATERIAL IS USED TO PRODUCE ANESTHESIA (SLEEP). TARGET ORGANS INCLUDE THE CENTRAL NERVOUS SYSTEM, RESPIRATORY SYSTEM, CARDIOVASCULAR SYSTEM & POSSIBLY THE FETUS.
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HOW SUPPLIED

Isoflurane, USP, is supplied in 100 mL amber-colored bottles (List 3292-49) and 250 mL amber-colored bottles (List 3292-51).

Storage: Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Isoflurane contains no additives and has been demonstrated to be stable at room temperature for five years.

Revised: October, 2004

References

1. JC Sill, *et al,* Anesthesiology 66:273-279, 1987
2. RF Hickey, *et al,* Anesthesiology 68:21-30, 1988
3. CW Buffington, *et al,* Anesthesiology 66:280-292, 1987
4. S Reiz, *et al,* Anesthesiology 59:91-97, 1983
5. S Slogoff and AS Keats, Anesthesiology 70:179-188, 1989
6. KJ Tuman, *et al,* Anesthesiology 70:189-198, 1989
7. DT Mangano, Editorial Views, Anesthesiology 70:175-178, 1989

Product of United Kingdom
Product inquiries should be directed to Hospira, Inc.
Lake Forest, IL 60045 USA

Manufactured by:
Hospira, Inc., Lake Forest, IL 60045 USA
Novation, the supply company of VHA and UHC, and NOVAPLUS are trademarks of Novation, LLC.

Printed in USA

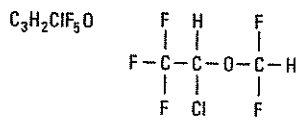
ISOFLURANE, USP

Liquid for Inhalation

NOVAPLUS® Rx only

DESCRIPTION

Isoflurane, USP, a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2, 2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$C_3H_2ClF_5O$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5°C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25°/25°C		1.496
Vapor pressure in mm Hg**	20°C	238
	25°C	295
	30°C	367
	35°C	450

**Equation for vapor pressure calculation:

$\log_{10}P_{vap} = A + \frac{B}{T}$ where: A = 8.056

B = -1664.58

T = °C + 273.16 (Kelvin)

Isoflurane, like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide which may result in elevated levels of carboxyhemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO_2 absorber canister at high flow rates over many hours or days. When a clinician suspects that CO_2 absorbent may be desiccated, it should be replaced before the administration of isoflurane.

As with other halogenated anesthetic agents, isoflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics (see CONTRAINDICATIONS).

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The

incidence of tur[illegible] these mice was the same as in untreated control mice wh[illegible]ere given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-

base derangements. (Con[illegible]rescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of Isoflurane, USP are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress. See PRECAUTIONS for information regarding malignant hyperthermia and elevated carboxyhemoglobin levels.

During marketing, there have been rare reports of mild, moderate and severe (some fatal) post-operative hepatic dysfunction and hepatitis.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by Isoflurane, USP and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This

may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100\, P_V F_V}{F_T (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxant may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

EN-0421

Product of Japan
Product inquiries should be directed to Abbott Laboratories, North Chicago, IL 60064, USA

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

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

(No. 4456) EN-0421 (11/04)-Rev. November, 2004

ULTANE®

sevoflurane

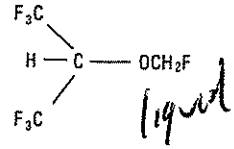
volatile liquid for inhalation

℞ only

NOVAPLUS™

DESCRIPTION

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



Sevoflurane, Physical Constants are:

Molecular weight	200.05
Boiling point at 760 mm Hg	58.6°C
Specific gravity at 20°C	1.520 - 1.525
Vapor pressure in mm Hg	157 mm Hg at 20°C
	197 mm Hg at 25°C
	317 mm Hg at 36°C

Distribution Partition Coefficients at 37°C:

Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47 - 54
Brain/Gas	1.15

Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly in Medical Applications:

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinylchloride	17.4
Polyethylene	1.3

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

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

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).

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