Isoflurane, USP

Inhalation Anesthetic for use in Horses and Dogs

- Isoflurane, USP is used for induction and maintenance of general anesthesia in horses and dogs.
- Clear, colorless, stable liquid containing no additives or chemical stabilizers.
- Nonflammable and nonexplosive.
- Only for use with a precision vaporizer calibrated for isoflurane.
- Available in 250 mL amber-colored bottles. Each mL contains 99.9% isoflurane.
- Backed by the Dechra Veterinary Technical and Sales Support Teams.

Dechra
Veterinary Products

To order, please contact your Dechra or distributor representative or call (866) 683-0660.
For more information, please visit www.dechra-us.com

Important Safety Information: As with all drugs, side effects may occur. Isoflurane, USP is contraindicated in horses and dogs with known sensitivity to isoflurane or to other halogenated agents. Isoflurane is a profound respiratory depressant. **RESPIRATION MUST BE MONITORED CLOSELY IN THE HORSE and DOG AND SUPPORTED WHEN NECESSARY. Operating rooms should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors.** To avoid production of carbon monoxide, isoflurane should not be passed through desiccated soda lime or barium hydroxide lime. Hypotension, respiratory depression and arrhythmias have been reported. Refer to the prescribing information for complete details or visit www.dechra-us.com.

24-hour Veterinary Technical Support available (866) 933-2472.
Nonurgent Technical Support available via email support@dechra.com.

Approved by FDA under ANADA # 200-129.
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

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Warning: Not for use in horses intended for food.

Isoflurane, USP

Inhalation Anesthetic

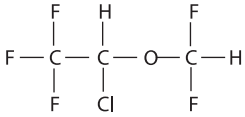
For Use in Horses and Dogs

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Isoflurane, USP is a nonflammable, nonexplosive general inhalation anesthetic agent. Its chemical name is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Each mL contains 99.9% isoflurane.
Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5°C
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: $A = 8.056$, $B = -1664.58$, $T = °C + 273.16$

Partition coefficients at 37°C:

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25°C - rubber and plastic:

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23°C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec.and 23°C	Greater than useful concentration in anesthesia

MAC (Minimum Alveolar Concentration) is 1.31% in horses[1] and 1.28% in dogs[6].

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime (at normal operating temperatures), and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

Isoflurane, USP is an inhalation anesthetic. Induction and recovery from anesthesia with isoflurane are rapid.[2,5] The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY IN THE HORSE AND DOG AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, both tidal volume and respiratory rate decrease.[3,6] This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure; however, heart rhythm is stable and cardiac output is maintained with controlled ventilation and normal $PaCO_2$ despite increasing depth of anesthesia. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia increases heart rate and raises cardiac output above levels observed with controlled ventilation.[3] Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog.

Muscle relaxation may be adequate for intra-abdominal operations at normal levels of anesthesia. However, if muscle relaxants are used to achieve greater relaxation, it should be noted that: ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane but does not reverse the direct neuromuscular depression of isoflurane.

INDICATIONS AND USAGE

Isoflurane, USP is used for induction and maintenance of general anesthesia in horses and dogs.

CONTRAINDICATIONS

Isoflurane, USP is contraindicated in horses and dogs with known sensitivity to isoflurane or to other halogenated agents.

WARNINGS

Increasing depth of anesthesia with isoflurane, USP may increase hypotension and respiratory depression. The electroencephalographic pattern associated with deep anesthesia is characterized by burst suppression, spiking, and isoelectric periods.[4]

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable percentage concentrations of isoflurane should be used (see DOSAGE AND ADMINISTRATION).

The action of nondepolarizing relaxants is augmented by isoflurane. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of isoflurane than in the presence of other commonly used anesthetics.

Not for use in horses intended for human consumption.

PRECAUTIONS

Isoflurane, like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide which may result in elevated carboxyhemoglobin levels 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.

Usage in Pregnancy: Reproduction studies have been performed in mice and rats with no evidence of fetal malformation attributable to isoflurane, USP. Adequate data concerning the safe use of isoflurane in pregnant and breeding horses and dogs have not been obtained.

ADVERSE REACTIONS

Hypotension, respiratory depression and arrhythmias have been reported.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Dechra at (866) 933-2472.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at http://www.fda.gov/reportanimalae.

OVERDOSAGE

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

Stop drug administration, establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

DOSAGE AND ADMINISTRATION

Caution: Operating rooms should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors.

Premedication: A premedication regimen, which may be employed depending upon the patient status, to avert excitement during induction, might include an anticholinergic, a tranquilizer, a muscle relaxant, and a short-acting barbiturate.

Inspired Concentration: The delivered concentration of isoflurane, USP should be known. Isoflurane may be vaporized using a flow-through vaporizer specifically calibrated for isoflurane. Vaporizers delivering a saturated vapor which then is diluted (e.g., Verni-trol® vaporizer) also may be used. 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 used (mL/min)

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

Induction:

Horses: Inspired concentrations of 3.0 to 5.0% isoflurane alone with oxygen following a barbiturate anesthetic induction are usually employed to induce surgical anesthesia in the horse.

Dogs: Inspired concentrations of 2.0 to 2.5% isoflurane alone with oxygen following a barbiturate anesthetic induction are usually employed to induce surgical anesthesia in the dog.

These concentrations can be expected to produce surgical anesthesia in 5 to 10 minutes.

Maintenance: The concentration of vapor necessary to maintain anesthesia is much less than that required to induce it.

Horses: Surgical levels of anesthesia in the horse may be sustained with a 1.5 to 1.8% concentration of isoflurane in oxygen.

Dog: Surgical levels of anesthesia in the dog may be sustained with a 1.5 to 1.8% concentration of isoflurane in oxygen.

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

Recovery from isoflurane anesthesia is typically uneventful.[2]

HOW SUPPLIED

Isoflurane, USP is packaged in 250 mL amber-colored bottles.

Storage: Store at room temperature 15° to 30°C (59° to 86° F).

Approved by FDA under ANADA # 200-129

References:

1. Steffey, E. P., Howland, D. Jr., Giri, S. and Eger, E.I.II.: Enflurane, Halothane and Isoflurane Potency in Horses. Am. J. Vet. Res. **38**(7): 1037-1039, 1977.
2. Auer, J. A., Garner, H.E., Amend, J.F., Hutcheson, D.P. and Salem, C.A.: Recovery from Anesthesia in Ponies: A Comparative Study of the Effects of Isoflurane, Enflurane, Methoxyflurane and Halothane. Equine Vet. J. **10**(1): 18-23, 1978.
3. Steffey, E.P., and Howland, D. Jr.: Comparison of Circulatory and Respiratory Effects of Isoflurane and Halothane Anesthesia in Horses. Am. J. Vet. Res. **41**(5): 821-825, 1980.
4. Auer, J.A., Amend, J.F., Garner, H.E., Hutcheson, D.P. and Salem, C.A.: Electroencephalographic Responses During Volatile Anesthesia in Domestic Ponies: A Comparative Study of Isoflurane, Enflurane, Methoxyflurane, and Halothane. Equine Practice **3**: 130-134, 1979.
5. Klide, A.M.: Cardiopulmonary Effects of Enflurane and Isoflurane in the Dog. Am. J. Vet. Res., Vol. 37, No. **2**: 127-131, 1976.
6. Steffey, E. P., Howland, D.: Isoflurane Potency in the Dog and Cat. Am. J. Vet. Res., Vol. 38, No. **11**: 1833-1836, 1977.

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Dechra

Sevoflurane

Inhalation Anesthetic

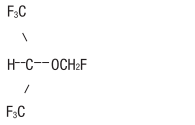
For Use in Dogs

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Sevoflurane, a volatile liquid, is a halogenated general inhalation anesthetic drug. Its chemical name 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 g/mL
Vapor pressure in mm Hg	at 20°C	157
	at 25°C	197
	at 36°C	317

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
Polyvinyl chloride	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 condition according to instructions.

INDICATIONS

Sevoflurane is indicated for induction and maintenance of general anesthesia in dogs.

DOSAGE AND ADMINISTRATION

Inspired Concentration: The delivered concentration of sevoflurane should be known. Since the depth of anesthesia may be altered easily and rapidly, only vaporizers producing predictable percentage concentrations of sevoflurane should be used. Sevoflurane should be vaporized using a precision vaporizer specifically calibrated for sevoflurane. Sevoflurane contains no stabilizer. Nothing in the drug product alters calibration or operation of these vaporizers. The administration of general anesthesia must be individualized based on the patient's response. **WHEN USING SEVOFLURANE, PATIENTS SHOULD BE CONTINUOUSLY MONITORED AND FACILITIES FOR MAINTENANCE OF PATENT AIRWAY, ARTIFICIAL VENTILATION, AND OXYGEN SUPPLEMENTATION MUST BE IMMEDIATELY AVAILABLE.**

Replacement of Desiccated CO_2 Absorbents: When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced. An exothermic reaction occurs when sevoflurane is exposed to CO_2 absorbents. This reaction is increased when the CO_2 absorbent becomes desiccated (see PRECAUTIONS).

Premedication: No specific premedication is either indicated or contraindicated with sevoflurane. The necessity for and choice of premedication is left to the discretion of the veterinarian. Preanesthetic doses for premedicants may be lower than the label directions for their use as a single medication.[1]

Induction: For mask induction using sevoflurane alone, inspired concentrations of **up to 7%** sevoflurane with oxygen are employed to induce surgical anesthesia in the healthy dog. These concentrations can be expected to produce surgical anesthesia in 3 to 14 minutes. **Due to the rapid and dose dependent changes in anesthetic depth, care should be taken to prevent overdosing. Respiration must be monitored closely in the dog and supported when necessary with supplemental oxygen and/or assisted ventilation.**

Maintenance: Sevoflurane may be used for maintenance anesthesia following mask induction using sevoflurane or following injectable induction agents. The concentration of vapor necessary to maintain anesthesia is much less than that required to induce it.

Surgical levels of anesthesia in the healthy dog may be maintained with inhaled concentrations of **3.7-4.0%** sevoflurane in oxygen in the absence of premedication and **3.3-3.6%** in the presence of premedication. The use of injectable induction agents without premedication has little effect on the concentrations of sevoflurane required for maintenance. Anesthetic regimens that include opioid, alpha2 -agonist, benzodiazepine or phenothiazine premedication will allow the use of lower sevoflurane maintenance concentrations.

CONTRAINDICATIONS

Sevoflurane is contraindicated in dogs with a known sensitivity to sevoflurane or other halogenated agents.

WARNINGS

Sevoflurane is a profound respiratory depressant.

DUE TO THE RAPID AND DOSE DEPENDENT CHANGES IN ANESTHETIC DEPTH, RESPIRATION MUST BE MONITORED CLOSELY IN THE DOG AND SUPPORTED WHEN NECESSARY WITH SUPPLEMENTAL OXYGEN AND/OR ASSISTED VENTILATION.

In cases of severe cardiopulmonary depression, discontinue drug administration, ensure the existence of a patent airway and initiate assisted or controlled ventilation with pure oxygen. Cardiovascular depression should be treated with plasma expanders, pressor agents, antiarrhythmic agents or other techniques as appropriate for the observed abnormality.

Due to sevoflurane's low solubility in blood, increasing the concentration may result in rapid changes in anesthetic depth and hemodynamic changes (dose dependent decreases in respiratory rate and blood pressure) compared to other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be corrected by decreasing or discontinuing the inspired concentration of sevoflurane.

Potassium hydroxide containing CO2 absorbents (e.g. BARALYME®) are not recommended for use with sevoflurane.

ADVERSE REACTIONS

The most frequently reported adverse reactions during maintenance anesthesia were hypotension, followed by tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis.

Infrequent adverse reactions include paddling, retching, salivation, cyanosis, premature ventricular contractions and excessive cardiopulmonary depression.

Transient elevations in liver function tests and white blood cell count may occur with sevoflurane, as with the use of other halogenated anesthetic agents.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Dechra at (866) 933-2472.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at www.fda.gov/reportanimalae.

PRECAUTIONS

Halogenated volatile anesthetics can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide (CO) that may result in elevated carboxyhemoglobin levels in some patients. To prevent this reaction, sevoflurane should not be passed through desiccated soda lime or barium hydroxide lime.

Replacement of Desiccated CO_2 Absorbents:

When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. The exothermic reaction that occurs with sevoflurane and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. Extremely rare cases of spontaneous fire in the respiratory circuit of the anesthesia machine have been reported during sevoflurane use in conjunction with the use of a desiccated CO_2 absorbent, specifically those containing potassium hydroxide (e.g. BARALYME®). Potassium hydroxide-containing CO_2 absorbents are not recommended for use with sevoflurane. An unusually delayed rise in the inspired gas concentration (decreased delivery) of sevoflurane compared with the vaporizer setting may indicate excessive heating of the CO_2 absorbent canister and chemical breakdown of sevoflurane. The color indicator of most CO_2 absorbent may not change upon desiccation. Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

The use of some anesthetic regimens that include sevoflurane may result in bradycardia that is reversible with anticholinergics. Studies using sevoflurane anesthetic regimens that included atropine or glycopyrrolate as premedicants showed these anticholinergics to be compatible with sevoflurane in dogs.

During the induction and maintenance of anesthesia, increasing the concentration of sevoflurane produces dose dependent decreases in blood pressure and respiratory rate. Due to sevoflurane's low solubility in blood, these 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. **RESPIRATION MUST BE MONITORED CLOSELY IN THE DOG AND SUPPORTED WHEN NECESSARY WITH SUPPLEMENTAL OXYGEN AND/OR ASSISTED VENTILATION.** The low solubility of sevoflurane also facilitates rapid elimination by the lungs.

The use of sevoflurane in humans increases both the intensity and duration of neuromuscular blockade induced by nondepolarizing muscle relaxants. The use of sevoflurane with nondepolarizing muscle relaxants has not been evaluated in dogs.

Compromised or debilitated dogs: Doses may need adjustment for geriatric or debilitated dogs. Because clinical experience in administering sevoflurane to dogs with renal, hepatic and cardiovascular insufficiency is limited, its safety in these dogs has not been established.

Breeding dogs: The safety of sevoflurane in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

Neonates: The safety of sevoflurane in young dogs (less than 12 weeks of age) has not been evaluated.

HUMAN SAFETY

Not for human use. Keep out of reach of children.

Operating rooms and animal recovery areas should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors.

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.

Direct exposure to eyes may result in mild irritation. If eye exposure occurs, flush with plenty of water for 15 minutes. Seek medical attention if irritation persists.

Symptoms of human overexposure (inhalation) to sevoflurane vapors include respiratory depression, hypotension, bradycardia, shivering, nausea and headache. If these symptoms occur, remove the individual from the source of exposure and seek medical attention.

The safety data sheet contains more detailed occupational safety information. To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Dechra at (866) 933-2472.

CLINICAL PHARMACOLOGY

Sevoflurane is an inhalational anesthetic agent for induction and maintenance of general anesthesia. The Minimum Alveolar Concentration (MAC) of sevoflurane as determined in 18 dogs is 2.36%.[2] MAC is defined as that alveolar concentration at which 50% of healthy patients fail to respond to noxious stimuli. Multiples of MAC are used as a guide for surgical levels of anesthesia, which are typically 1.3 to 1.5 times the MAC value.

Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient at 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. During sevoflurane induction, there is a rapid increase in alveolar concentration toward the inspired concentration.

Sevoflurane produces only modest increases in cerebral blood flow and metabolic rate, and has little or no ability to potentiate seizures.[3] Sevoflurane has a variable effect on heart rate, producing increases or decreases depending on experimental conditions.[4, 5] Sevoflurane produces dose-dependent decreases in mean arterial pressure, cardiac output and myocardial contraction.[6] Among inhalation anesthetics, sevoflurane has low arrhythmogenic potential.[7]

Sevoflurane is chemically stable. No discernible degradation occurs in the presence of strong acids or heat. Sevoflurane reacts through direct contact with CO_2 absorbents (soda lime and barium hydroxide lime) 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.

Compound A:

The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (potassium hydroxide and/or NaOH) forming an alkene (Compound A) from sevoflurane.

Compound A is produced when sevoflurane interacts with soda lime or barium hydroxide lime. Reaction with barium hydroxide lime results in a greater production of Compound A than does reaction with soda lime. Its concentration in a circle absorber system increases with increasing sevoflurane concentrations and with decreasing fresh gas flow rates. 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 the quantities of CO_2 absorbed, which in turn will depend on fresh gas flow in the anesthetic circle system, metabolic status of the patient and ventilation. Although Compound A is a dose-dependent nephrotoxin in rats, the mechanism of this renal toxicity is unknown. Two spontaneously breathing dogs under sevoflurane anesthesia showed increases in concentrations of Compound A as the oxygen flow rate was decreased at hourly intervals, from 500 mL/min (36 and 18 ppm Compound A) to 250 mL/min in (43 and 31 ppm) to 50 mL/min (61 and 48 ppm).[8]

Fluoride ion metabolite:

Sevoflurane is metabolized to hexafluoroisopropanol (HFIP) with release of inorganic fluoride and CO_2. Fluoride ion concentrations are influenced by the duration of anesthesia and the concentration of sevoflurane. 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 humans, the fluoride ion half-life was prolonged in patients with renal impairment, but human clinical trials contained no reports of toxicity associated with elevated fluoride ion levels. In a study in which 4 dogs were exposed to 4% sevoflurane for 3 hours, maximum serum fluoride concentrations of 17.0-27.0 mcmole/L were observed after 3 hours of anesthesia. Serum fluoride fell quickly after anesthesia ended, and had returned to baseline by 24 hours post-anesthesia.

In a safety study, eight healthy dogs were exposed to sevoflurane for 3 hours/day, 5 days/week for 2 weeks (total 30 hours exposure) at a flow rate of 500 mL/min in a semiclosed, rebreathing system with soda lime. Renal toxicity was not observed in the study evaluation of clinical signs, hematology, serum chemistry, urinalysis, or gross or microscopic pathology.

DRUG INTERACTIONS

In the clinical trial, sevoflurane was used safely in dogs that received frequently used veterinary products including steroids and heartworm and flea preventative products.

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 other inhalational anesthetics. Sevoflurane is compatible with benzodiazepines and opioids as commonly used in surgical practice.

Phenothiazines and Alpha$_2$-Agonists: Sevoflurane is compatible with phenothiazines and alpha$_2$-agonists as commonly used in surgical practice. In a laboratory study, the use of the acepromazine/oxymorphone/thiopental/sevoflurane anesthetic regimen resulted in prolonged recoveries in eight (of 8) dogs compared to recoveries from sevoflurane alone.

CLINICAL EFFECTIVENESS

The effectiveness of sevoflurane was investigated in a clinical study involving 196 dogs. Thirty dogs were mask-induced with sevoflurane using anesthetic regimens that included various premedicants. During the clinical study, one hundred sixty-six dogs received sevoflurane maintenance anesthesia as part of several anesthetic regimens that used injectable induction agents and various premedicants.

The duration of anesthesia and the choice of anesthetic regimens were dependent upon the procedures that were performed. Duration of anesthesia ranged from 16 to 424 minutes among the individual dogs. Sevoflurane vaporizer concentrations during the first 30 minutes of maintenance anesthesia were similar among the various anesthetic regimens. The quality of maintenance anesthesia was considered good or excellent in 169 out of 196 dogs.

The table shows the average vaporizer concentrations and oxygen flow rates during the first 30 minutes for all sevoflurane maintenance anesthesia regimens:

Average Vaporizer Concentrations among Anesthetic Regimens	Average Vaporizer Concentrations among Individual Dogs	Average Oxygen Flow Rates among Anesthetic Regimens	Average Oxygen Flow Rates among Individual Dogs
3.31-3.63%	1.6-5.1%	0.97-1.31 L/minute	0.5-3.0 L/minute

During the clinical trial, when a barbiturate was used for induction, the times to extubation, sternal recumbency and standing recovery were longer for dogs that received anesthetic regimens containing two preanesthetics compared to regimens containing one preanesthetic. Recovery times were shorter when anesthetic regimens used sevoflurane or propofol for induction. The quality of recovery was considered good or excellent in 184 out of 196 dogs.

Anesthetic regimen drug dosages, physiological responses, and the quality of induction, maintenance and recovery were comparable between 10 sighthounds and other breeds evaluated in the study. During the clinical study there was no indication of prolonged recovery times in the sighthounds.

HOW SUPPLIED

Sevoflurane is packaged in amber colored bottles containing 250 mL sevoflurane.

STORAGE CONDITIONS

Store at 20° to 25ºC (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86ºF). See USP controlled room temperature.

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1. Plumb, D.C. ed., Veterinary Drug Handbook, Second Edition, University of Iowa Press, Ames, IA: p. 424 (1995).
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