Why Piramal Critical Care?

- A leading manufacturer of inhaled anesthetics worldwide
- Dependable supplier of animal health products for more than a decade
- Market leader for veterinary Isoflurane in US
- Market leader for human Isoflurane in US[1]
- Piramal Critical Care products are used in more than 100 countries around the world[2]
- Piramal Sevoflurane is used in more than 26[3,#] million procedures per year
- Piramal Sevoflurane[2] and Isoflurane are stable for 5 years
- Manufactured from start to finish at our facility in Bethlehem, Pennsylvania[α]
- Manufacturing facility registered with and regularly inspected by the US FDA[2]

The Trusted choice *Globally*

Piramal Critical Care

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Bethlehem, PA 18017, USA
Toll Free No.: +1-800-414-1901
www.piramalcriticalcare.com

MKT-PIR-0010 AUG 2018

"Critical Care Solutions. Delivered."

- For additional details, please refer to the attached full prescribing information.
- Adverse events should be reported to Piramal Critical Care at http://pcc-chex.force.com/SiteComplaintForm.

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2. Data on file.
3. Piramal Critical Care estimates.
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7. US FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.
8. https://onlinelibrary.wiley.com/doi/pdf/10.1002/3527600418.mb26675466e4316. Accessed on 11th June '2018.
9. Refer attached Isoflurane Prescribing Information under the topic maintenance.
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11. Data on file. Drop Test Lab Report Piramal Critical Care Controlled Documents, 18 June 2014.
12. Compliance of Glass Packaging with Human and Environmental Health and Safety Toxics-in-Packaging Requirements. Mahinka S.P.et al., February 8,2013.
13. http://apsf.org/newsletters/html/2008/winter/20_minrad_packaging.htm. Accessed on 8th August 2018.
14. As per section "How supplied" of Petrem® prescribing information (The package insert describes the bottle as amber in colour, making it semi-transparent).
15. Glass is completely recyclable (http://environment.about.com/od/recycline/a/benefits_of_glass_recycling.htm) - accessed on April 4, 2018.
16. International Safe Transit Association, an ANSI Accredited Standards Developer.
17. ISTA 1A 2014 Non-Simulation Integrity Performance Tests: Packaged-Products Weighing 150 lb (68 kg) or Less.
α: In select markets like USA and EU. #: Assumption of 1 hour average duration per procedure.
*: In select markets e.g. USA, UK etc.

They're all looking to you.
You can look to us.

Piramal Critical Care

Delivering quality animal health products for more than a decade.

Piramal Critical Care

Petrem®

(Sevoflurane, USP)

An inhalation anesthetic indicated for induction and maintenance of general anesthesia, for use in dogs.

Isoflurane, **USP**

An inhalation anesthetic indicated for induction and maintenance of general anesthesia, for use in horses and dogs.

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 material safety data sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call (888) 822-8431.

CLINICAL PHARMACOLOGY

Sevoflurane is an inhalational anesthetic agent for induction and maintenance of general anesthesia. The Minimum Alveolar Concentration (MAC) of sevoflurane, USP 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 (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 semi-closed, 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, USP 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% L/minute	1.6-5.1%	0.97-1.31 L/minute	0.5-3.0

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

Petrem® (sevoflurane, USP) is packaged in 100 mL and 250 mL amber colored bottles.

100 mL NDC 66794-018-10

250 mL NDC 66794-018-25

Storage Conditions

Store at 20° to 25°C (68°F to 77°F); excursions permitted to 15°C-30°C(59°F-86°F) [See USP Controlled Room Temperature]

REFERENCES

1. Plumb, D.C. ed., Veterinary Drug Handbook, Second Edition, University of Iowa Press, Ames, IA: p. 424 (1995).
2. Kazama, T. and Ikeda, K., Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology. 68: 435-437 (1988).
3. Scheller, M.S., Nakakimura, K., Fleischer, J.E. and Zornow, M.H., Cerebral effects ofsevoflurane in the dog: Comparison with isoflurane and enflurane. Brit. J. Anesthesia 65:388-392 (1990).
4. Frink, E.J., Morgan, S.E., Coetzee, A., Conzen, P.F. and Brown, B.R., Effects of sevoflurane, halothane, enflurane and isoflurane on hepatic blood flow and oxygenation in chronically instrumented greyhound dogs. Anesthesiology 76: 85-90 (1992).
5. Kazama, T. and Ikeda, K., The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. J. Anesthesiology 2: 63-8 (1988).
6. Bernard, J. M., Wouters, P.F., Doursout, M.F., Florence, B., Chelly, J.E. and Merin, R.G., Effects of sevoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 72:659-662 (1990).
7. Hayaski, Y., Sumikawa, K., Tashiro, C., Yamatodani, A. and Yoshiya, I., Arrhythmogenic threshold of epinephrine during sevoflurane, enflurane and isoflurane anesthesia in dogs. Anesthesiology 69: 145-147 (1988).
8. Muir, W.W. and Gadawski, J., Cardiorespiratory effects of low-flow and closed circuit inhalation anesthesia, using sevoflurane delivered with an in-circuit vaporizer and concentrations of compound A. Amer. J. Vet. Res. 59 (5): 603-608 (1998).

ANADA 200-438, Appoved by FDA

Manufacturer by:
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Bethlehem, PA 18017
(888) 822-8431

AWN-34599704

MKT-PIR-0010 AUG 2018

Piramal Critical Care

Petrem®

(Sevoflurane, USP)

For induction and maintenance of general anesthesia in dogs.

- Therapeutically equivalent[6]
- Low blood-gas solubility[4]
- Precise control of anesthetic levels[4]
- Well tolerated[4]
- Cardiovascular protection[5]

Petrem®

(Sevoflurane, USP)

For induction and maintenance of general anesthesia in dogs.

Petrem® is therapeutically equivalent to the branded Sevoflurane product

The FDA reviewed the data submitted in support of the Petrem® Sevoflurane formulation and determined that it was chemically equivalent and therefore therapeutically equivalent to the branded product.[6]

Petrem® is the first generic Sevoflurane approved for veterinary use[6]

Water Content: The draft USP Monograph for Sevoflurane allows for up to 1,000 ppm of water. Sevoflurane formulations containing between 1 and 999 ppm water will produce the same clinical and therapeutic effects. Petrem® contains approximately 65 ppm.[7]

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

Adverse Reactions: Hypotension, tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis have been reported.

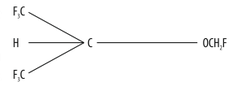
- #**For additional details, please refer to the attached full prescribing information.**
- #**Adverse events should be reported to Piramal Critical Care at http://pcc-chex.force.com/SiteComplaintForm.**

DESCRIPTION

Inhalation Anesthetic For Use in Dogs

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

Petrem® (sevoflurane, USP), 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	Vapor pressure in mm Hg at 20°C	157
Boiling point at 760 mm Hg	58.6°C	at 25°C	197
Specific gravity at 20°C	1.520 - 1.525 g/mL	at 36°C	317

Distribution Partition Coefficients at 37°C:		Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly in Medical Applications:	
Blood/Gas	0.63-0.69	Conductive rubber	14.0
Water/Gas	0.36	Butyl rubber	7.7
Olive Oil/Gas	47-54	Polyvinyl chloride	17.4
Brain/Gas	1.15	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

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

DOSAGE AND ADMINISTRATION

Inspired Concentration: The delivered concentration of Petrem 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 P RECAUTIONS).

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 mus t be monitored closely in the dog and supported when necessary with s upplemental oxygen and/or assisted ventilation.

Maintenance: Petrem 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, $alpha_2$ - agonist, benzodiazepine or phenothiazine premedication will allow the use of lower sevoflurane maintenance concentrations.

CONTRAINDICATIONS

Petrem 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 CO_2 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.

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 afer 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 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 (decrease 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 anes thetic 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

Warning: Not for use in horses intended for food

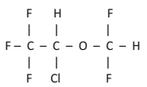
Isoflurane, USP

Inhalation Anesthetic For Veterinary 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 (uncorr.)
Refractive index $n\frac{20}{D}$	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)

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[3] and 1.28% in dogs[5].

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 abo ve 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 intraabdominal 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

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 food.

Keep out of reach of children.

PRECAUTIONS

Isoflurane, USP, like 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, USP.

Usage in Pregnancy: Reproduction studies have been performed in mice and rats with no evidence of fetal malformation attributable to isoflurane. 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.

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 flowthrough vaporizer specifically calibrated for Isoflurane. Vaporizers delivering a saturated vapor which is then diluted (e.g., Vernitrol® vaporizer) also may be used. The delivered concentration from such a vaporizer may be calculated using the formula:

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

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 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.

Dogs: 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 (NDC 66794-013-25) amber-colored bottle.

Storage:

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

References

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2. Auer, J.A., Garner, H.E., Amend, J.F., Hutcheson, D.P. and Salem, C.A.:
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Equine Vet. J. 10(1): 18-23 1978.

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5. Klide, A.M.:
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Distributed by:

Piramal Critical Care, Inc.
3950 Schelden Circle, Bethlehem, PA 18017
(888) 822-8431.

To report adverse reactions or obtain MSDS, call (888) 822-8431.

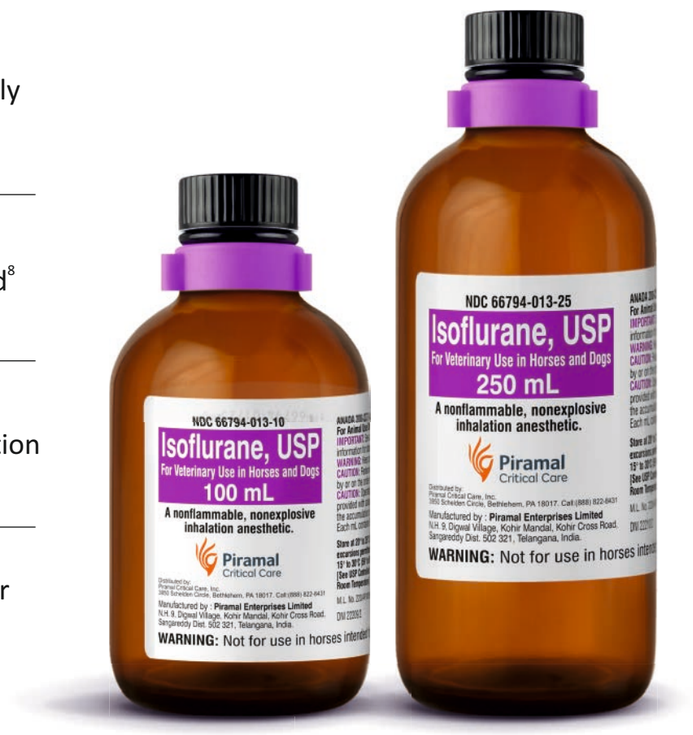
MKT-PIR-0010 AUG 2018

Piramal Critical Care

Isoflurane, USP

For induction and maintenance of general anesthesia in horses and dogs.

- Therapeutically equivalent
- Well tolerated[8]
- Ease of induction
- Cardiovascular protection



Isoflurane, USP

For induction and maintenance of general anesthesia in horses and dogs.

Trusted by millions of Physicians

- Piramal has 66% market share for human Isoflurane in US[1]
- 50% global market share by volume[1]

Your trusted inhalation anesthetic

- Recovery is uneventful[9]
- No reported organ damage in humans or animals[10]
- Available in two sizes, 100 ml and 250 ml

Piramal Isoflurane has a 5 year shelf life

Warning: Not for use in horses intended for food.

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

Adverse Reactions: Hypotension, respiratory depression and arrhythmias have been reported.

- **#For additional details, please refer to the attached full prescribing information.**
- **#Adverse events should be reported to Piramal Critical Care at http://pcc-chex.force.com/SiteComplaintForm.**

Piramal Critical Care

Glass - by choice

Conclusion of a drop test conducted on Sevoflurane screw cap bottles from Piramal, by an independent testing agency.

The drop test was conducted by an independent laboratory, using a modified ISTA protocol.[11]

- **Two sets of drops were conducted-one with empty bottles and the others filled with 250ml of liquid, replicating the weight and volume of a 250ml bottle of Sevoflurane. All bottles were dropped 8 times.**
- **None of the empty bottles broke during the drop test.**
- **None of the filled bottles broke until at least the third drop of the prescribed 8-drop sequence.**
- **The breakage rate of bottles, whether empty or filled, was under 1%.**
- **The failure rate of filled bottles, was under 2%.**
- **98.1% of filled bottles displayed no visual damage.**

MKT-PIR-0010 AUG 2018

Advantages of Piramal Sevoflurane and its glass packaging

Quality & Trust

- Glass bottles and vials have been the most trusted form of packaging for pharmaceuticals for hundreds of years because of its inert properties[12]
- Glass has been the primary choice for packaging all halogenated ether anesthetics, and has been used by all anesthetic gas manufacturers[13]
- Piramal Sevoflurane has been used by anesthesiologists for over 10 years[2]
- Piramal Sevoflurane is manufactured in a cGMP compliant site in the USA, inspected periodically by the US FDA and UK MHRA[2]

Stability

- Piramal Sevoflurane has a 5 year shelf life[2,*]

Semi-transparent

- The semi-transparency of the Type III amber-coloured glass used to package Piramal Sevoflurane allows for easy monitoring of its contents[14]

Recyclable/Environmentally Friendly

- Piramal Sevoflurane bottle packaging is environmentally friendly[15]

Strength

- Chances of breakage with Piramal glass bottles are as low as 1%,[11] based on the Drop test conducted by an independent laboratory, using a modified ISTA[16] protocol[17]

Quality[2] ...Stability[2] ...Semi-transparent[14] & Recyclable/Environmentally Friendly[15]...