Prescribing Information

ENFLURANE®

(enflurane)

Inhalation Anesthetic

AbbVie Corporation
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Saint-Laurent (Qc) Canada H4S IZ1

Control # 158312

DATE OF PREPARATION:
November 1, 2012

DATE OF PREVIOUS REVISION:

DATE OF REVISION:

NAME OF DRUG

ENFLURANE®

(enflurane)

THERAPEUTIC CLASSIFICATION

Inhalation Anesthetic

ACTIONS AND CLINICAL PHARMACOLOGY

ENFLURANE®(enflurane), a halogenated methylethyl ether, is an inhalation anesthetic. Induction and recovery from ENFLURANE® anesthesia are rapid. ENFLURANE® does not appear to stimulate excessive salivation or tracheo-bronchial secretions, or affect bronchomotor tone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired ENFLURANE® concentration. This property would be predicted based upon its Oswald partition coefficients.

ENFLURANE® reduces ventilation as depth of anesthesia increases. This is a result of a decrease in tidal volume with rate of respiration remaining essentially constant. ENFLURANE® provokes a sigh response reminiscent of diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. A slight fall in cardiac output, stroke volume, and peripheral resistance, and an increase in central venous pressure may occur. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Electrocardiographic monitoring and recording indicate that the cardiac rhythm remains remarkably stable. Elevation of carbon dioxide level in arterial blood does not alter cardiac rhythm.

ENFLURANE® has been shown to sensitize the myocardial conduction system to epinephrine, and serious arrhythmias including ventricular fibrillation have occurred in dogs.

However, studies in human subjects indicate that there is a certain margin of safety in the administration of epinephrine-containing solutions during ENFLURANE® anesthesia. ENFLURANE® anesthesia has been used in medical conditions involving high levels of endogenous catecholamines, as well as surgical procedures involving carefully administered quantities of epinephrine-containing solutions. On the basis of this experience, up to 10 mL of 1:100,000 or 1:200,000 epinephrine-containing solution alone or in conjunction with lidocaine 0.5% to 2% may be injected subcutaneously at a rate of not more than 10 mL/10 minute period and no more than 30 mL/hour.

The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ENFLURANE® anesthesia. This effect of lidocaine is dose related. More dilute solutions

and reduced dosages should be used in highly vascular areas. All customary precautions in the use of vasoconstrictor substances should be observed, including monitoring of respiration, blood pressure and pulse. Epinephrine should not be used in association with ENFLURANE® in patients with hyperthyroidism, or in patients with pre-existing cardiac disease who cannot tolerate the tachycardia or hypertension which may result from the administration of exogenous catecholamines.

Epinephrine should be used in association with ENFLURANE® only in patients who have adequate pulmonary function to ensure optimal pulmonary ventilation.

Muscle relaxation in man may in certain cases be adequate for intra-abdominal operations at normal levels of anesthesia. Should greater relaxation be necessary, minimal doses of muscle relaxants may be used. NONDEPOLARIZING MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED BY ENFLURANE®. All commonly used muscle relaxants are compatible with ENFLURANE®. Neostigmine does not reverse the direct relaxant effect of ENFLURANE®.

ENFLURANE® 0.25% to 1.0% (average 0.5%) provides analgesia equal to that produced by 30% to 60% (average 40%) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither ENFLURANE® nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither ENFLURANE® nor nitrous oxide when used for obstetrical analgesia alters BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with ENFLURANE®.

Analgesic doses of ENFLURANE®, up to approximately 1.0%, do not significantly depress the rate or force of uterine contraction during labour and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1.0% and 2.0% delivered ENFLURANE®; concentrations somewhere between 2.0% and 3.0% delivered ENFLURANE® may abolish uterine contractions.

ENFLURANE® displaces the myometrial response curve to oxytocin so that at lower concentrations of ENFLURANE® oxytocin will restore uterine contractions; however, as the dose of ENFLURANE® progresses (somewhere between 1.5% and 3.0% delivered ENFLURANE®) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when ENFLURANE® is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see **DOSAGE AND ADMINISTRATION**).

Mean estimated blood loss in patients anesthetized for therapeutic termination of pregnancy with 1.0% ENFLURANE® in 70% nitrous oxide with oxygen is approximately twice that noted following therapeutic termination of pregnancy followed with the use of a local anesthetic technique (40 mL versus 20 mL).

Pharmacokinetics: Biotransformation of ENFLURANE® in man results in low peak levels of serum fluoride averaging 15 mcgmol/L. These levels are well below the 50 mcgmol/L threshold level which can produce minimal renal damage in normal subjects. However, patients

chronically ingesting isoniazid or other hydrazine-containing compounds may metabolize greater amounts of ENFLURANE®. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 mcgmol/L, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged ENFLURANE® anesthesia in man in the absence of surgery. Thus ENFLURANE® does not depress this aspect of the immune response.

INDICATIONS AND CLINICAL USE

ENFLURANE®(enflurane) may be used for induction and maintenance of general anesthesia. ENFLURANE® may be used to provide analgesia for vaginal delivery. Low concentrations of ENFLURANE® (see **DOSAGE AND ADMINISTRATION**) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of ENFLURANE® may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

ENFLURANE®(enflurane) is contraindicated in patients with pre-existing EEG abnormalities or seizure disorders (see **WARNINGS**).

ENFLURANE® is contraindicated in patients with known sensitivity to enflurane or to other halogenated agents.

ENFLURANE® is contraindicated in patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration (see **WARNINGS**).

ENFLURANE® is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia, or in patients with a known or suspected history of malignant hyperthermia.

WARNINGS

With increasing depth of ENFLURANE®(enflurane) anesthesia, central nervous system excitation occurs, manifested by a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes, interspaced with periods of electrical silence, and may show frank seizure-like activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by hyperventilation producing low arterial carbon dioxide tension. The pattern serves as a warning that depth of anesthesia is excessive. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity.

Cerebral blood flow and metabolism studies in normal volunteers during the changes in the EEG patterns show no evidence of cerebral hypoxia, and recovery appears to be uncomplicated. Nevertheless, ENFLURANE® should not be used in patients with convulsive disorders.

Since levels of anesthesia may be altered easily and rapidly, only vaporizers which deliver predictable concentrations should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

The action of nondepolarizing relaxants is augmented by ENFLURANE®, so less than usual amounts of those drugs should be used. The recovery time from the myoneural effect of these relaxants is greater in the presence of ENFLURANE® than for other commonly used anesthetics. Safety of repeated anesthesia with ENFLURANE® has not been established.

Epinephrine containing solutions should be used in association with ENFLURANE® only in patients with adequate pulmonary function and should not be used in patients with hyperthyroidism or in patients with pre-existing cardiac disease who cannot tolerate the tachycardia or hypertension which may result from the administration of exogenous catecholamines.

When previous exposure to a halogenated anesthetic is known to have been followed by evidence of unexplained hepatic dysfunction, consideration should be given to use of an agent other than ENFLURANE®.

As with other halogenated anesthetics, ENFLURANE® may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**). Therefore, appropriate alternative anesthetic agent(s) should be considered, this is especially important in patients with pre-existing hepatic conditions.

Isolated cases of increased carboxyhemoglobin have been reported with the use of halogenated inhalation agents with a $-CF_2$ moiety (i.e., desflurane, enflurane and isoflurane). No clinically significant concentrations of carbon monoxide are produced in the presence of normally hydrated absorbents. Care should be taken to follow manufacturer's instructions for CO_2 absorbents.

Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during administration of general anesthesia with drugs in this class when used in conjunction with desiccated CO_2 absorbents, specifically those containing potassium hydroxide (e.g. Baralyme). When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of ENFLURANE®. The color indicator of most CO_2 absorbents does not necessarily change as a result of 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.

PRECAUTIONS

General: ENFLURANE®(enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

ENFLURANE® as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 to 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for several days following administration.

Pregnancy: Safe use in pregnancy other than for analgesia for obstetrical use has not been established.

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 ENFLURANE® is administered to a nursing woman.

Laboratory tests: Bromsulphalein (BSP) retention is mildly elevated postoperatively in some cases. Elevation of glucose and white blood cell count was observed postoperatively in paediatric patients. Glucose elevation should be considered in diabetic patients. Elevation of BUN, SGOT, LDH and OCT, have been also reported in the post-operative period following ENFLURANE® anesthesia in some pediatric patients.

ENFLURANE® should be used cautiously with pre-existing renal impairment.

Malignant Hyperthermia: In susceptible individuals, ENFLURANE® 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.). The syndrome of malignant hyperthermia secondary to ENFLURANE® appears to be rare. 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 ENFLURANE®, 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 derangement. Renal failure may appear later, and urine flow should be sustained if possible.

Drug Interactions: The action of nondepolarizing relaxants is augmented by ENFLURANE®. 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 neuromuscular blockade will be longer in the presence of ENFLURANE® than when halothane or nitrous oxide with a balanced technique are used.

ADVERSE REACTIONS

The following adverse reactions have been observed during ENFLURANE®(enflurane) administration:

- Malignant hyperthermia (see **PRECAUTIONS**).
- Hypotension, respiratory depression and hypoxia.
- Arrhythmias, shivering, nausea and vomiting.
- Elevation of glucose.
- Elevation of the white blood cell count.

Deep planes of anesthesia and hyperventilation producing hypocapnia may produce muscle twitching and/or seizures. There were rare reports of delayed convulsions.

Elevation of BUN, SGOT, LDH, OCT, alkaline phosphatase and bilirubin, with or without jaundice have been reported in the post-operative period following ENFLURANE® anesthesia in some patients. The relationship to ENFLURANE® has not been established.

Delirium, hallucinations and hiccups occur rarely.

Unexplained mild, moderate and severe liver injury including hepatic failure may rarely follow anesthesia with ENFLURANE®. Serum transaminases may be increased and histologic evidence of injury may be found. The histologic changes are neither unique nor consistent. In several of these cases, it has not been possible to exclude ENFLURANE® as the cause or as a contributing cause of liver injury. The incidence of unexplained hepatotoxicity following the administration of ENFLURANE® is unknown, but it appears to be rare and not dose related.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with ENFLURANE®(enflurane) will generally produce marked hypotension and apnea in the absence of muscle relaxants. In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

1. Stop drug administration;
2. Establish that the airway is clear;
3. Instigate assisted or controlled ventilation with pure oxygen as the circumstances dictate.

Similarly, motor activity and increased electrical and seizure-like activity in the electroencephalogram may be indicative of excessive levels of anesthesia. In the event that this

occurs, it is recommended that the level of anesthesia be lowered. If motor activity does not cease, the administration of ENFLURANE® should be discontinued.

DOSAGE AND ADMINISTRATION

The concentration of ENFLURANE®(enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a) vaporizers calibrated specifically for ENFLURANE® and b) vaporizers from which delivered flows can easily and readily be calculated.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ENFLURANE® and that ENFLURANE® does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using ENFLURANE® alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ENFLURANE® mixture. In general, inspired concentrations of 2.0% to 4.5% ENFLURANE® produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5% to 3.0% ENFLURANE®. Maintenance concentrations should not exceed 3.0%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35 mmHg to 45 mmHg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ENFLURANE® 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 should be corrected by lightening the level of anesthesia.

Analgesia: ENFLURANE® 0.25% to 1.0% provides analgesia for vaginal delivery equal to that produced by 30% to 60% nitrous oxide. These concentrations normally do not produce amnesia.

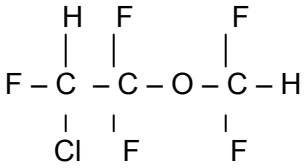
Cesarean Section: ENFLURANE® should ordinarily be administered in the concentration range of 0.5% to 1.0% to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the **ACTIONS AND CLINICAL PHARMACOLOGY** section.

PHARMACEUTICAL INFORMATION

CHEMISTRY:

Proper Name: ENFLURANE®

Structural Formula:



Molecular Formula: $C_3H_2ClF_5O$

Molecular Weight: 184.49

Chemical Name:

2-chloro-1,1,2-trifluoroethyl difluoromethyl ether

Description:

ENFLURANE® is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mmHg, and the vapour pressure (in mmHg) is 180 at 20°C, 225 at 25°C, and 355 at 37°C.

Vapour pressures can be calculated using the equation:

$1og_{10}P_{vap} = A + (B/T)$

A = 7.967, B = -1678.4, T = °C + 273.16 (Kelvin)

The specific gravity is 1.517 at 25°C.

The refractive index at 20°C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. ENFLURANE® is a clear, colourless, stable liquid whose purity exceeds 99.9%. No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. ENFLURANE® is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of ENFLURANE® at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

AVAILABILITY OF DOSAGE FORMS

ENFLURANE®(enflurane) is packaged in 125 mL and 250 mL amber-coloured bottles.

Storage Recommendation:

Store between 15° to 25°C. ENFLURANE® contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.