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 (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management). Renal failure may appear later, and urine flow should be sustained if possible.

Perioperative Hyperkalemia

Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Drug Interactions

Concomitant use of succinylcholine with inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with nondepolariz-ing agents. Neostigmine reverses the effects of nondepolarizing muscle relaxants but has no effect on the relaxant properties of isoflurane itself. All commonly used muscle relaxants are compatible with isoflurane.

Beta-sympathomimetic agents like isoprenaline and alpha- and betasympathomimetic agents like adrenaline and noradrenaline should be used with caution during isoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Inducers of CYP2E1

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to significant increases in plasma fluoride concentrations.

Concomitant use of isoflurane and isoniazide can increase the risk of potentiation of the hepatotoxic effects.

Isoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates.

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.

Opioids, benzodiazepines and other sedative agents are associated with respiratory depression. Caution should be exercised when these agents are concomitantly administered with isoflurane.

Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for 2-4 days after anesthesia with isoflurane. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

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

serious undesirable effects include malignant hyperthermia, hyperkalemia, elevated serum creatine kinase, and myoglobinuria (see WARNINGS AND PRECAUTIONS).

Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anesthetic drugs including isoflurane.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received.

Bronchospasm and laryngospasm due to airway irritation have been reported with volatile anesthetics during inhalation. Electroencephalographic changes and convulsions have been observed with isoflurane.

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 N2O in adults.

Isolated cases of increased carboxyhemoglobin have been reported with the use of fluorinated inhalation agents (i.e., desflurane, enflurane and isoflurane).

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding.

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

Transient increases in blood bilirubin, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances.

Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anesthetic agents,

including isoflurane. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The etiology of anaphylactic reactions experienced during inhalational anesthetic exposure is, however, unclear because of the exposure to multiple concomitant drugs, many of which are known to cause such reactions.

Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

Hypotension and respiratory depression have been observed. Close monitoring of blood pressure and respiration is recommended. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of anesthesia.

DOSAGE AND ADMINISTRATION

Vaporizers specially calibrated for isoflurane should be used so that the concentration of anesthetic delivered can be accurately controlled.

General Anesthesia

MAC values for isoflurane diminish with age, falling from an average in oxygen of 1.28% in the mid-twenties to 1.15% in the mid-forties, to 1.05% in the mid-sixties age group. For neonatesthe MAC of isoflurane in oxygen is 1.6%, in infants aged 1 month to 6 months is 1.87%, and from 6 months to 12 months, 1.80%.

Premedication

Drugs used for premedication should be selected for the individual patient, bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice.

Induction

A short-acting barbiturate or other intravenous induction agent is usually administered followed by inhalation of the isoflurane mixture. Alternatively, isoflurane with oxygen or with an oxygen/nitrous oxide mixture may be used.

It is recommended that induction with isoflurane be initiated at a concentration of 0.5%. Concentrations of 1.5 to 3.0% usually produce surgical anesthesia in seven to ten minutes.

Maintenance

Surgical levels of anesthesia may be maintained with 1.0 to 2.5% isoflurane in oxygen/nitrous oxide mixtures. An additional 0.5 to 1.0% isoflurane may be required when given with oxygen alone. If added relaxation is required, supplemental doses of muscle relaxant may be used.

Arterial pressure levels during maintenance tend to be inversely related to alveolar isoflurane concentrations in the absence of other complicating factors. Excessive falls in blood pressure may be due to depth of anesthesia and, in these circumstances, should be corrected by reducing the inspired isoflurane concentration.

Elderly

As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anesthesia in elderly patients. See above for MAC values.

Sedation

Sedation may be maintained with 0.1 to 1.0% isoflurane in air/oxygen mixtures. This dose will need to be titrated to the requirements of the individual patients.

STORAGE

Isoflurane contains no additives and has been demonstrated to be stable at room temperature (15° to 30°C) for periods in excess of five years.

HOW SUPPLIED

Isoflurane is supplied in bottles containing 100 mL. (List number B506).

Manufactured by:
Aesica Queenborough Limited,
Queenborough, Kent ME11 5EL,
United Kingdom.

For:
AbbVie Inc.,
North Chicago, IL 60064-4000, USA

Marketed by:
Getz Pharma (Pvt.) Limited
Karachi, Pakistan.

Date of Revision of the Text: February 2014

FORANE®

(ISOFLURANE)

Inhalation
Anaesthetic

1000007515

DESCRIPTION

Isoflurane, a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug with a mildly pungent ethereal odor. No additive or stabilizer is present. It is identified chemically as 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its molecular weight is 184.5. Its structural formula is:

Some physical constants are:

Boiling point 760 mmHg	48.5°C	
Refractive index $n_{D\,20}$	1.2990 – 1.3005	
Specific gravity 25°/25°C	1.496	
Vapor pressure in mmHg	18°C	218
	20°C	238
	22°C	261
	24°C	285
	25°C	295
	26°C	311
	30°C	367
	35°C	450

Equation for vapor pressure calculation:

$\text{Log}_{10} P_{vap} = A + B/T$

where A = 8.056
B = - 1664.58
T = °C + 273.16 (Kelvin)

Partition coefficients @ 37° C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.80

Partition coefficients @ 25° C--
Rubber and plastic:

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0

Polyethylene/gas approx.	2.0
Polyurethane/gas approx.	1.4
Polyolefin/gas approx.	1.1
Butyl acetate/gas approx.	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

M.A.C. (minimum alveolar concentration) in man:

Age	100% Oxygen	70% N_2
0 – 1 mo. (neonate)	1.60%	
1 – 6 mos.	1.87%	
6 – 12 mos.	1.80%	
26 ± 4 yrs.	1.28%	0.56%
44 ± 7 yrs.	1.15%	0.50%
64 ± 5 yrs.	1.05%	0.37%

Samples stored in stability chambers in amber glass for five years, as well as samples directly exposed for seven days to accelerated light conditions 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.

PHARMACOLOGIC PROPERTIES

Induction and, particularly, recovery are rapid. Although slight pungency may limit the rate of induction, excessive salivation and tracheobronchial secretions are do not appear to be stimulated. Pharyngeal and laryngeal reflexes

are diminished quickly. Levels of anesthesia may be changed rapidly with isoflu-rane. Heart rhythm remains stable. Spontaneous respiration becomes depressed as depth of anesthesia increases and should be closely monitored and supported when necessary.

During induction there is a decrease in blood pressure which returns towards normal with surgical stimulation.

Blood pressure tends to fall during maintenance in direct relation to depth of anesthesia, but cardiac rhythm remains stable. With controlled respiration and normal $PaCO_2$, cardiac output tends to be maintained despite increasing depth of anesthesia primarily through a rise in heart rate which compensates for a reduction in stroke volume. With spontaneous respiration, theresulting hypercapnia may increase heart rate and cardiac output above awake levels.

Cerebral blood flow remains unchanged during light isoflurane anesthesia but tends to rise at deeper levels. Increases in cerebrospinal fluid pressure may be prevented or reversed by hyperventilating the patient before or during anesthesia.

Electroencephalographic changes and convulsions are extremely rare with isoflurane. In general, isoflurane produces an EEG pattern similar to that seen with other volatile anesthetics.

Isoflurane appears to sensitize the myocardium to adrenaline. Limited data suggest that subcutaneous infiltration of up to 50 mL of 1:200,000 solution adrenaline does not induce ventricular arrhythmias in patients anesthetized with isoflurane.

Muscular relaxation may be adequate for some intra-abdomi-nal operations at normal levels of anesthesia, but should greater relaxation be required small doses of intravenous muscle relaxants may be used.

Isoflurane may be used for the induction and maintenance of general anesthesia. Adequate data are not available to establish its place in pregnancy.

Relatively little metabolism of isoflurane occurs in the human body. In the postoperative period only 0.17% of the isoflurane taken up can be recovered as urinary metabolites. Peak seruminorganic fluoride values usually

average less than 5 micromole/litre and occur about four hours after anesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after isoflurane administration.

Known metabolites of isoflurane have been found to be either nontoxic or present in too low a concentration to be harmful.

INDICATIONS

Isoflurane may be used for induction and maintenance of general anesthesia. This anesthetic agent can also be used for sedation of ventilated patients in the intensive therapy unit for up to 48 hours.

CONTRAINDICATIONS

Isoflurane is contraindicated in patients with known sensitivity to isoflurane or other halogenated anesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS AND PRECAUTIONS

Isoflurane markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations and flow rates should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering isoflurane to patients at risk for QT prolongation.

Caution should be exercised in administering general anesthesia, including isoflurane, to patients with mitochondrial disorders. Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using isoflurane during obstetric anesthesia. Consideration should be taken to use the

lowest possible concentration of isoflurane in obstetrical operations.

Isolated cases of increased carboxyhemoglobin have been reported with the use of fluorinated inhalation agents (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 manufacturers' 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 Isoflurane. 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

As with any potent general anesthetic, isoflurane should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Since levels of anesthesia may be altered quickly and easily with isoflurane, only vaporizers which deliver a predictable output with reasonable accuracy, or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory depression may provide some indication of anesthetic depth.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances. It has been reported that previous exposure to halogenated hydrocarbon anesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Regardless of the anesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease.

As with other halogenated agents, isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary.

The action of non-depolarizing relaxants is markedly potentiated with isoflurane.

Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur.

Isoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.

Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2-4 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Pregnancy and Lactation

Reproduction studies have been carried out on animals after repeated exposure to anesthetic concentrations of isoflurane. Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses six times the human dose. Studies with the rat demonstrated no effect on fertility, pregnancy or delivery or on the viability of the off-spring. No evidence of teratogenicity was revealed. Comparable experiments in rabbits produced similar negative results. The relevance of

these studies to the human is not known, as there are no adequate and well-controlled studies in pregnant women. Isoflurane should only be used during pregnancy if the benefit outweighs the potential risk.

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using isoflurane during obstetric anesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

Use in Cesarean Section

Isoflurane, in concentrations up to 0.75%, has been shown to be safe and efficacious for the maintenance of anesthesia for cesarean section.

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.

Children Under Two Years of Age

Isoflurane may be used in neonates and infants under two years of age with an acceptable margin of efficacy and safety and is compatible with all drugs commonly used in anesthetic practice.

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 pressures. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. There have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment includes discontinuance of triggering agents (e.g. isoflurane), intravenous administration of