SUMMARY OF PRODUCT CHARACTERISTICS

PROPRIETARY NAME (and dosage form)

FORANE® liquida

COMPOSITION

Each bottle contains the active ingredient, isoflurane, only. No additive or stabilizer is present.

PHARMACOLOGICAL CLASSIFICATION

N01AB06 - Anaesthetics

PHARMACOLOGICAL ACTION

Induction and, particularly, recovery are rapid. Although slight pungency may limit the rate of induction, excessive salivation and tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are diminished quickly. The levels of anaesthesia may be changed rapidly with isoflurane. Heart rhythm remains stable. Spontaneous respiration becomes depressed as depth of anaesthesia 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 anaesthesia, but cardiac rhythm remains stable. With controlled respiration and normal $PaCO_2$, cardiac output tends to be maintained despite increasing depth of anaesthesia primarily through a rise in heart rate, which compensates for a reduction in stroke volume. With spontaneous respiration, the resulting hypercapnia may increase heart rate and cardiac output above awake levels.

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

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

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-abdominal operations at normal levels of anaesthesia, 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 anaesthesia. 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 serum inorganic fluoride values usually average less than 5 micromole/litre and occur about four hours after anaesthesia, 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.

Paediatric Clinical Safety

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness. In addition, more recent published registry studies did not confirm these findings.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life (see PRECLINICAL SAFETY DATA). Clinical Overview R&D/17/0800

PRECLINICAL SAFETY DATA

Published studies in pregnant and juvenile animals suggest that the use of anaesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes. The clinical significance of these nonclinical findings is yet to be determined (see PHARMACOLOGIC PROPERTIES, Paediatric Clinical Safety). Clinical Overview R&D/17/0800

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS and SPECIAL PRECAUTIONS

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

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

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

Caution should be exercised in administering general anaesthesia, including **FORANE**, to patients with mitochondrial disorders.

FORANE, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using **FORANE** during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of **FORANE** 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 anaesthesia machine have been reported during administration of general anaesthesia with medicines 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 **FORANE**. The colour indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the colour indicator.

General

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

Since levels of anaesthesia may be altered quickly and easily with **FORANE**, 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 anaesthetic depth.

Reports demonstrate that **FORANE** 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 anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

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

As with other halogenated agents, **FORANE** 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 **FORANE**.

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

FORANE 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.

FORANE, as well as other general anaesthetics, may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see ***Effects on Ability to Drive and Use Machines***).

Children Under Two Years of Age

FORANE 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 medicines commonly used in anaesthetic practice.

Malignant Hyperthermia

In susceptible individuals, **FORANE** anaesthesia 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 anaesthesia, 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. **FORANE**), intravenous administration of 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 anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric 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.

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 anaesthesia with **FORANE**. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

INTERACTIONS

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

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

Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during **FORANE** 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*~~ Heading removed because not all the text that follows is related to this interaction.

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

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

FORANE 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 anaesthetics 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 **FORANE**.

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 sub-therapeutic doses. Studies with the rat demonstrated no effect on fertility, pregnancy or delivery or on the viability of the offspring. 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. In line with CCDS

FORANE should only be used during pregnancy if the benefit outweighs the potential risk.

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

Published animal studies of some anesthetic/sedation drugs have reported adverse effects on brain development in early life (see **PRECLINICAL SAFETY DATA**). Clinical Overview R&D/17/0800

Use in Caesarean Section

FORANE, in concentrations up to 0.75 %, has been shown to be safe and efficacious for the maintenance of anaesthesia for caesarean section.

Lactation

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when **FORANE** is administered to a nursing woman.

DOSAGE AND DIRECTIONS FOR USE

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

General Anaesthesia

MAC (minimum alveolar concentration) values for **FORANE** diminish with age. The table below indicates average MAC values for different age groups.

Age	**Average MAC Value in 100 % Oxygen**	**70 % N_2O**
Preterm neonates < 32 weeks gestational age	1.28 %	
Preterm neonates 32-37 weeks gestational age	1.41 %	
0 – 1 month (neonate)	1.60 %	
1 – 6 months	1.87 %	
6 – 12 months	1.80 %	
1 – 5 years	1.60 %	
26 ± 4 years	1.28 %	0.56 %
44 ± 7 years	1.15 %	0.50 %
64 ± 5 years	1.05 %	0.37 %

Premedication

Medicines used for premedication should be selected for the individual patient, bearing in mind the respiratory depressant effect of **FORANE**. The use of anticholinergic medicines is a matter of choice.

Induction

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

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

Maintenance

Surgical levels of anaesthesia may be maintained with 1.0 to 2.5 % **FORANE** in oxygen/nitrous oxide mixtures. An additional 0.5 to 1.0 % **FORANE** 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 **FORANE** concentrations in the absence of other complicating factors. Excessive falls in blood pressure may be due to depth of anaesthesia and, in these circumstances, should be corrected by reducing the inspired **FORANE** concentration.

Geriatric

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

Sedation

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

SIDE-EFFECTS

Adverse reactions encountered in the administration of **FORANE** 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 SPECIAL PRECAUTIONS**)**.**

Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anaesthetic medicines including **FORANE**.

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 anaesthetics during inhalation.

Electroencephalographic changes and convulsions have been observed with **FORANE**.

FORANE potentiates the muscle relaxant effect of all muscle relaxants, most notably non-depolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O in adults.

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

FORANE, 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 anaesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

Reports demonstrate that **FORANE** 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 anaesthetic agents, including **FORANE**. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The etiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the exposure to multiple concomitant medicines, many of which are known to cause such reactions.

Minimally raised levels of serum inorganic fluoride occur during and after **FORANE** anaesthesia, 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In the event of overdosage, or what may appear to be overdosage, stop medicine 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 anaesthesia.

IDENTIFICATION

FORANE is a non-flammable liquid.

PRESENTATION

FORANE is supplied in 100 mℓ and 250 mℓ amber coloured bottles.

STORAGE INSTRUCTIONS

Store below 25 °C.

FORANE contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Keep cap tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION DETAILS

Kenya: 17847

NAFDAC Regn. No: 04-493

Zambia: 128/015

Uganda: 9404/01/16

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