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pharma

דצמבר 2017

Isoflurane USP, Terrell TM

רופא/ה, רוקח/ת נכבד/ה,
חברת פארמה מדיס בע"מ מבקשת להודיע על החמרות ועדכונים בעלון לרופא של התכשיר שבנדון.
בהודעה זו מצוינים השינויים המהווים החמרה, מסומנים בקו תחתון. בעלון קיימים שינויים נוספים שאינם מהווים החמרה.

הרכב התכשיר- מרכיב פעיל: Isoflurane 100%

התוויה מאושרת:

Isoflurane is indicated as a general anaesthetic by inhalation.

החמרות בעלון לרופא נעשו בסעיפים הבאים:

4.4. Special warnings and precautions for use

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 anaesthesia, 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 judgement should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations (please refer to section 4.6).

Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during the administration of general anaesthesia 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 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

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. Cirrhosis, viral hepatitis or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary.

Use of isoflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. A lower concentration of isoflurane is recommended for use in these patients.

Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. Small changes in moods and symptoms may persist for up to 6 days after administration. This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery (please refer to section 4.7).

A potentiation of neuromuscular fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis. Isoflurane should be used with caution in these patients.

Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur (see section 4.8).

Isoflurane may cause respiratory depression which may be augmented by narcotic premedication or other agents causing respiratory depression.

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see section 4.8).

Children Under Two Years of Age
Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group.

Malignant Hyperthermia

There have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Perioperative hyperkalaemia

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 post-operative 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 hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

4.5 Interactions with Other medicinal products and Other Forms of Interaction

Combinations advised against:
Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic 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. Treatment should be stopped 15 days prior to surgery.

Combinations requiring precautions in using:
Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives): Risk of peri- operative hypertension. In patients undergoing elective surgery, treatment should ideally be discontinued several days before surgery.

Adrenaline, by subcutaneous or gingival injections: risk of serious ventricular arrhythmia as a consequence of increased heart rate, although the myocardial sensitivity with respect to adrenaline is lower with the use of isoflurane than in the case of halothane.

Cardiovascular compensation reactions may be impaired by beta-blockers.

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.

Use of isoflurane and isoniazid can increase the risk of potentiation of the hepatotoxic effects.

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

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, and caution should be exercised when concomitantly administered with isoflurane

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 pediatric patients during the post-operative period.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarizing agents. Neostigmine has an effect on the non-depolarising relaxants, but has no effect on the relaxing action of isoflurane itself.

4.6 Fertility, pregnancy and lactation

Use in Caesarean Section
Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anaesthesia for caesarean section (please refer to section 4.4).

4.7 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 isoflurane. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see Section 4.4).

4.8 Undesirable Effects

a. Summary of the safety profile

Potential serious undesirable effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, myoglobinuria, anaphylactic reactions and liver adverse reactions (please refer to section 4.4 and 4.8). Shivering, nausea, vomiting , ileus, agitation and delirium have been observed in the post-operative period.

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

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

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post- marketing experience. Frequency cannot be estimated from the available data, therefore it is "not known".

SUMMARY OF MOST FREQUENT ADVERSE DRUG REACTIONS		
SOC	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Not known	Carboxyhaemoglobinaemia[2]
Immune system disorder	Not known Not known	Anaphylactic reaction[1] Hypersensitivity[1]
Metabolism and nutrition disorders	Not known Not known	Hyperkalaemia[2] Blood glucose increased
Psychiatric disorders	Not known Not known Not known	Agitation Delirium Mood
Nervous system disorders	Not known Not known	Convulsion Mental impairment[4]
Cardiac disorders	Not known Not known Not known Not known Not known Not known	Arrhythmia Bradycardia Cardiac arrest Electrocardiogram QT prolonged Tachycardia Torsade de pointes
Vascular disorders	Not known Not known	Hypotension[2] Haemorrhage[3]
Respiratory, thoracic and mediastinal disorders	Not known Not known Not known	Bronchospasm[2] Dyspnoea[1] Wheezing[1]

	Not known Not known	Respiratory depression[2] Laryngospasm[2]
Gastrointestinal disorders	Not known Not known Not known	Ileus Vomiting
Hepatobiliary disorders	Not known Not known Not known	Hepatic necrosis[2] Hepatocellular injury[2] Blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known Not known Not known	Swelling face[1] Dermatitis contact[1] Rash[1]
Renal and urinary disorders	Not known Not known	Blood creatinine increased Blood urea decreased
General disorders and administration site conditions	Not known Not known Not known	Hyperthermia malignant[2] Chest discomfort[1] Chills
Investigations	Not known Not known Not known Not known Not known Not known	White blood cell count increased[1] Hepatic enzyme increased[2] Fluoride increased[1] Electroencephalogram abnormal Blood cholesterol decreased Blood alkaline phosphatase decreased
Musculoskeletal and connective tissue disorders	Not known Not known	Myoglobinuria Rhabdomyolysis

[1]See section 4.8(c)
[2]See section 4.4
[3]In patients undergoing induced abortion. See section 4.4.
[4]May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See section 4.4.
[5]Small changes in moods and symptoms may persist for up to 6 days. See section 4.4.

c. **Description of selected adverse reactions**

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

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 isoflurane. 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 drugs, many of which are known to cause such reactions.

Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anaesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed (mean 4.4 µmol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

d. **Paediatric population**

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 post-operative period. (See section 4.4.)

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See section 4.4.)

e. **Other special populations**

Neuromuscular disease:

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 post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4).

Elderly:

Lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. (See section 4.2.).

4.9 Overdose

As with other halogenated anaesthetics, 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.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פנייה לבעל הרישום:
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