Module 1 : Administrative information
1.3. Product information

1.3.1. Summary of product characteristics (SmPC)

Enclosed herewith

Summary of Product Characteristics

ISOTROY 250 (ISOFLURANE USP)

1. Name of Medicinal Product:

Isotroy 250

Isoflurane USP

2. Qualitative and quantitative composition:

Each bottle contains:
Isoflurane USP……..…250 ml

For full of excipients, please refer section 6.1.

3. Pharmaceutical Form:

Liquid for inhalation.

A clear, colourless liquid.

4. Clinical Particulars:

4.1 Therapeutic indications:

ISOTROY (Isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

4.2 Posology and method of administration:

Premedication

Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by isoflurane, and the heart rate tends to be increased. The use of anti cholinergic drugs is a matter of choice.

Inspired Concentration

The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a. Vaporizers calibrated specifically for isoflurane;

b. Vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor, which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100\ Pv\ \ Fv}{FT\ (PA\ PV)}$$

Where:

PA = Pressure of atmosphere
PV = Vapor pressure of isoflurane
FV = Flow of gas through vaporizer (mL/min)
FT = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction

Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance

Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

4.3 Contraindications:

Known sensitivity to isoflurane, or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings and precautions for use:

WARNINGS:

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 creatinine 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.

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 pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected by an elevated temperature, increased usage of the CO2, pH decrease, etc. Treatment includes discontinuance of triggering agents (e.g., isoflurane), 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 derangements. Renal failure may appear later, and urine flow should be sustained if possible.

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

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

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.

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.

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

Isoflurane like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide, which may result in elevated levels of carboxyhemoglobin 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.

As with other halogenated anesthetic agents, isoflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics.

Laboratory Tests

Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

4.5 Interaction with other medicinal products and other forms of interaction:

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 N_2O.

4.6 Pregnancy and lactation:

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

4.7 Effects on ability to drive and use machines:

Not known.

4.8 Undesirable effects:

Adverse reactions encountered in the administration of isoflurane are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.
Shivering, nausea, vomiting and ileus have been observed in the postoperative period.
As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.
During marketing, there have been rare reports of mild, moderate and severe (some fatal) postoperative hepatic dysfunction and hepatitis.
Isoflurane has also been associated with perioperative hyperkalemia.
There have been rare post-marketing reports of hepatic failure and hepatic necrosis associated with the use of potent volatile anesthetic agents, including isoflurane. Due to the spontaneous nature of these reports, the actual incidence and relationship of isoflurane to these events cannot be established with certainty.

Acute Myocardial Infarction:
In the treatment of acute myocardial infarction, the following adverse events were reported: Bradycardia, Hypotension, Bronchospasm, Heart Failure, Heart Block, Supraventricular Tachycardia, Atrial Fibrillation, Atrial Flutter, Ventricular Tachycardia, Cardiac Reinfarction, Nonfatal Cardiac Arrests, Cardiogenic Shock, Ventricular Septal Defect, Development of Mitral Regurgitation, Renal Failure, Pulmonary Embolism.

During post marketing experience with atenolol, the following have been reported in temporal relationship to the use of the drug:
elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbance, sick sinus

syndrome, and dry mouth. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.
In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of atenolol.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of betaadrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with
atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

4.9 Overdose:

Overdosage with atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely. The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause and bradycardia. Additionally, common effects associated with overdosage

of any beta-adrenergic blocking agent and which might also be expected in atenolol overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENSICARD can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include :

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A β2 stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

CLINICAL PHARMACOLOGY

Isoflurane is an inhalation anesthetic. The MAC (minimum alveolar concentration) is as follows:

Age	100% Oxygen	70 % N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency, which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant.

RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY.

As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

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. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO2, cardiac output is maintained despite increasing depth of anesthesia, primarily through an increase in heart rate, which compensates for a reduction in stroke volume. The hypercapnia, which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants.

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. All commonly used muscle relaxants are compatible with isoflurane.

5.2 Pharmacokinetic properties:

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5.3 Preclinical safety data:

Not applicable

6. Pharmaceutical particulars:

6.1 List of excipients:

No excipients are used in the formulation.

6.2 Incompatibilities:

Not applicable

6.3 Shelf-life:

48 months

6.4 Special precautions for storage:

Store between 15°C and 30°C.

6.5 Nature and contents of container:

250 ml amber colour glass bottle with 25 mm black colour cap with plastic U plug and ring pull-small (plastic purple colour collar).

7. Marketing authorization holder:

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Bodakdev, Ahmedabad-380054, India
Ph No.: +9179 26856242/43/44/45
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8. Marketing authorization number:

B4-4388

9. Date of first authorization/ renewal of authorization:

26th February 2015

10. Date of revision of the text:

Not Applicable