SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Halothane 100% Inhalation Vapour, Liquid.

2. QUALITATIVE AND QUANTITATIVE COMPOSIT ION

Halothane BP 100% v/v.

The finished product is comprised only of the active ingredient, see section 6.1

3. PHARMACEUTICAL FORM

Inhalation Liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Induction and maintenance of general anaesthesia in adults and children. Use of halothane in paediatric dental anaesthesia should be restricted to hospitals only (see contraindications, section 4.3)

4.2. Posology and Method of Administration

Posology

Adults
Induction: Anaesthesia may be induced with 2 to 4% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen. Induction may also be started at a concentration of 0.5% v/v and increased gradually to the required level.

Maintenance: Anaesthesia is maintained with concentrations of 0.5 to 2% depending on the flow rate used; the lower concentration is usually suitable for the elderly.

Children:
For induction in children a concentration of 1.5 to 2% v/v has been used.

Elderly:
Elderly patients tend to require less halothane than adults but the actual

dose is dependent on the patient's physical state.

Method of administration

See section 6.6

4.3 Contraindications

History of unexplained jaundice or pyrexia after a previous exposure to halothane is an absolute contra-indication to its future use in that patient.
Halothane is contraindicated in patients with known, or suspected, genetic predisposition to malignant hyperpyrexia. (see 4.4)
Children under 18 years undergoing dental procedures outside hospital (see 4.4)

4.4. Special Warnings and Special Precautions for Use

Halothane can induce liver damage. Minor changes in serum amino-transferase activity have been reported to occur in up to 30% of patients. The incidence of severe liver damage (jaundice, which may lead to hepatic failure as a consequence of massive hepatic cell necrosis) is much rarer but cases requiring liver transplants and fatalities have been reported. The risk of developing hepatic failure appears to be greatly increased by repeated exposure to halothane. Although short intervals of time between exposures are likely to increase the risk of hepatotoxicity, even long intervals between exposure may not reduce the risks, since some patients have developed severe reactions to halothane given many years after the previous exposure. *Other* risk factors for hepatotoxicity include female gender, obesity, middle age and a history of drug allergy. On present available information, the following precautions should be taken:

1. A careful anaesthetic history is to be taken from patients due to undergo anaesthesia in order to determine whether exposure to halothane took place and the nature of any adverse reaction to this agent.

2. History of unexplained jaundice or pyrexia after a previous exposure to halothane is an absolute contraindication to its future use in that patient.

3. Further exposure to halothane within three months is to be avoided unless there are overriding reasons for its re-use.

4. Patients who have exhibited adverse reactions to halothane should be informed and strictly instructed to alert their physician. Details of the reaction should be entered on the patient's medical records.

A rise in CSF and/or intracranial pressure might occur during neurosurgery, the effects of which may be mitigated by the use moderate hyperventilation.

Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

As with other agents of this type, halothane anaesthesia has been shown to trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperpyrexia. This is more common when halothane is co-administered with suxamethonium. The syndrome includes nonspecific features such as hypercapnia, muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias and unstable blood pressure. An increase in overall metabolism may be reflected in an elevated temperature. Treatment includes discontinuation of triggering agents, administration of dantrolene sodium and application of supportive therapy.

During the induction of halothane anaesthesia, a moderate fall in blood pressure commonly occurs. (Halothane lowers arterial blood pressure in a dose-dependent manner). The pressure tends to rise when the vapour concentration is reduced to maintenance levels, but it usually remains steady below the pre-operative level. This hypotensive effect is useful in providing a clear operating field and a reduction in haemorrhage. However, if necessary, intravenous doses of methoxamine *(5* mg are usually adequate) can be given to counteract the fall in blood pressure.

Anaesthesia with halothane may be associated with bradycardia, which may augment its hypotensive effect. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to be predominant or when halothane is used in conjunction with other agents likely to cause a bradycardia.

Halothane should be used with caution in patients with:

- Phaeochromocytoma
- Renal failure
- Pre-existing liver disease
- Myasthenia gravis
- Porphyria

Paediatric population

Arrhythmias are very common in children anaesthetised with halothane. Children anaesthetised with halothane should have ECG, blood pressure, oxygen saturation and end tidal CO_2 monitoring in a setting where full resuscitative equipment is available and with staff fully trained in the resuscitation of children. The presence of additional arrhythmogenic factors especially hypoxia and carbon dioxide retention, use of

sympathomimetics (see 4.5), and other factors which may stimulate the sympathetic nervous system should also be taken into account. Thus, to prevent hypoxia, inhalational anaesthetics are given with concentrations of oxygen greater than 21%.

Use of inhaled anaesthetic agents has been associated with very rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in children during the postoperative period. The condition has been described in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. Use of suxamethonium has been associated with most, but not all of these cases. These patients showed evidence of muscle damage with increased serum creatine kinase concentration and myoglobinuria. These patients did NOT have classical signs of malignant hyperthermia such as muscle rigidity, rapid increase in body temperature, or increased oxygen uptake and carbon dioxide production. Prompt and vigorous treatment for hyperkalaemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.

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

The incidence of cardiac arrhythmias may be increased when adrenaline, most other sympathomimetics (e.g. methylphenidate), and theophylline are used concurrently with halothane. There is also an increased risk of hypertension when volatile liquid anaesthetics are given with methylphenidate.
The use of beta-adrenoceptor antagonists during halothane anaesthesia is at the discretion of the anaesthetist. The risk of arrhythmias is also increased if halothane is used in patients receiving dopaminergics (e.g. levodopa).

Muscle relaxants: All commonly used muscle relaxants may be used in conjunction with halothane, but, as halothane potentiates the actions of gallamine and D-Tubocurarine, the doses of these muscle relaxant must be reduced. The association of D-Tubocurarine with halothane may lead to a marked fall in blood pressure.

Ganglion blocking agents: Potentiation occurs between halothane and hypotensive agents such as pentolinium and trimetaphan. These drugs must be used in reduced dosage when administered in conjunction with halothane.

Halothane, along with all other general anaesthetics, may interact with aminoglycoside antibiotics resulting in respiratory depression. This effect may be potentiated by the concurrent use of a neuromuscular blocker.

The concurrent use of suxamethonium with halothane is not advisable due

to the increased possibility of hyperpyrexia.

Morphine and chlorpromazine increase the depressant effects of halothane on respiration.

The effects of both ergometrine and oxytocin on the parturient uterus are diminished by halothane.

An enhanced hypotensive effect may be seen when general anaesthetics are given with adrenergic neurone blockers, alpha-blockers, antipsychotics or calcium channel blockers.
Monoamine oxidase inhibitors (MAOIs) should normally be stopped 2 weeks before surgery because of hazardous interactions between general anaesthetics and MAOIs.

4.6. Fertility, pregnancy and lactation

Pregnancy:

Studies in animals have shown reproductive toxicity (see section 5.3). Halothane reduces uterine muscle tone during pregnancy and generally its use is not recommended in obstetrics because of the increased risk of postpartum haemorrhage.

Breastfeeding:

Traces of halothane have been detected in breast milk. Breast feeding should be withheld for 24 hours after halothane anaesthesia.

4.7. Effects on ability to drive and use machines

Patients should not drive, or operate machinery, until fully recovered; i.e. for at least 24 hours after receiving halothane.

4.8. Undesirable effects

The following undesirable effects have been reported following the use of halothane:

Hepatic necrosis, also known as “Halothane hepatitis” (see section 4.4) occurs rarely but fatalities have been reported. Severe hepatotoxicity occurs more frequently after repeated exposure to halothane.

Eosinophilia has been reported in conjunction with halothane induced hepatotoxicity.

Malignant hyperpyrexia has occasionally been reported with halothane, as with other halogenated anaesthetics. (see 4.4)

Cardiac arrhythmias are very common during halothane anaesthesia. Ventricular arrhythmias occur more frequently than with other volatile anaesthetic agents (see
4.4). There have been instances of cardiac arrest.

As with other halogenated anaesthetics, halothane has a depressant effect on the respiratory and cardiovascular systems and the following undesirable effects have been reported:

Respiratory depression
Hypotension (see 4.4)
Bradycardia (see 4.4)
Skeletal muscle relaxation
Post-operative nausea, vomiting and shivering.
Renal failure, sometimes with concurrent liver failure

Adverse reactions have been spontaneously reported during post-approval use of Halothane. These events are reported voluntarily from a population with an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events.

Summary of Post-Marketing Adverse Drug Reactions	
System Organ	**Adverse Reactions**
Cardiac disorders	Bradycardia Intraoperative Cardiac arrest in patient with extraocular cystices Ventricular extrasystole Idioventricular rhythm
Hepatobiliary disorders	Fulminant Hepatic Failure Acute toxic hepatitis

4.9. Overdose

Overdose is unlikely under normal circumstances. However, should it occur, halothane administration should cease immediately and the patient ventilated mechanically until blood gases return to an acceptable level. Signs of overdose are bradycardia and profound hypotension.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, general; Halogenated hydrocarbons

ATC code: N01 AB01

Volatile inhalational anaesthetic which causes vasodilation, bradycardia and hypotension.

5.2. Pharmacokinetic properties

Halothane is absorbed on inhalation, anaesthesia being induced in about *5* minutes. Recovery is usually rapid but is dependent on the concentration of halothane used and the length of anaesthesia.

Halothane is largely (60-80%) excreted unchanged by the lungs, but variable amounts are metabolised by the liver. Urinary metabolites include trifluoroacetic acid, bromide and chloride ions. Other metabolites may be implicated in halothane hepatoxicity. Halothane also diffuses across the placenta.

5.3. Pre-clinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings in not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

None.

6.2. Incompatibilities

Vaporiser: Halothane must not be used in the EMO ether vaporiser as it attacks the metal; a vaporiser specially constructed for halothane should be used.

6.3. Shelf life

60 months (unopened)

6.4. Special precautions for storage

Store in a dark place below 30°C. Keep well closed.

6.5. Nature and contents of container

Amber glass bottle with red collar and an aluminum gold lacquered cap fitted with a polythene wad (contact face polyethylene terephthalate).
Pack size: 250 ml

6.6. Special precautions for disposal and other handling

None stated.

7. MARKETING AUTHORISATION HOLDER

Piramal Pharma Limited.

8. MARKETING AUTHORISATION NUMBER(S)

NA

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

NA

10. DATE OF REVISION OF THE TEXT

07/2023