APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PROPOFOL MCT/LCT 1 % (20 mL) FRESENIUS

PROPOFOL MCT/LCT 1 % (50 mL) FRESENIUS

PROPOFOL MCT/LCT 1 % (100 mL) FRESENIUS

Emulsion for injection or infusion

2. QUALITITATIVE AND QUANTITATVE COMPOSITION

Each mL emulsion contains 10 mg propofol.

Each 20 mL ampoule/vial contains 200 mg propofol.

Each 50 mL vial contains 500 mg propofol.

Each 100 mL vial contains 1 000 mg propofol.

Excipients with known effect:

1 mL emulsion contains:

soya-bean oil, refined 50 mg

sodium, max. 0,06 mg

Contains sugar (as glycerol 22,5 mg/mL)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion.

White homogeneous emulsion.

Do not use if two layers can be seen after shaking the emulsion.

pH of emulsion: 7,5 – 8,5

Osmolality of emulsion: 300 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROPOFOL MCT/LCT 1 % FRESENIUS is a short-acting intravenous general anaesthetic medicine for:

- Induction and maintenance of general anaesthesia as part of a balanced anaesthetic technique.
- Sedation of artificially ventilated patients in the Intensive Care Unit (ICU) for a period of up to 72 hours.
- Conscious sedation for surgical and diagnostic procedures in adults, provided that there are adequate facilities for monitoring of haemodynamic and oxygenation parameters and if administered by a qualified anaesthetist.

4.2 Posology and method of administration

Supplementary analgesics are required in addition to PROPOFOL MCT/LCT 1 % FRESENIUS, where analgesia is required.

Posology

A. ADULTS

Induction of general anaesthesia

PROPOFOL MCT/LCT 1 % FRESENIUS may be used to induce anaesthesia by slow bolus injection or infusion.

In unpremedicated and premedicated patients:

Most adult patients aged less than 55 years are likely to require 1,5 mg/kg to 2,5 mg/kg (0,15 mL/kg - 0,25 mL/kg) of PROPOFOL MCT/LCT 1 % FRESENIUS, (approximately 4 mL every 10 seconds in an average healthy adult) by slow bolus injection or infusion titrated against the response of the patient until clinical signs show onset of anaesthesia. The total dose required can be reduced by lower rates of administration (20 mg/min - 50 mg/min [2 mL/min - 5 mL/min]).

Over the age of 55 years the requirement will generally be less. In patients of ASA (American Society of Anaesthesiologists) Grades 3 and 4, lower rates of administration should be used (approximately 20 mg [2 mL] every 10 seconds).

Maintenance of general anaesthesia

Anaesthesia can be maintained by administering PROPOFOL MCT/LCT 1 % FRESENIUS either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia.

Infusion:

The average rate of administration varies between patients, but rates in the region of 4 mg/kg/h to 12 mg/kg/h (0,4 mL/kg/h – 1,2 mL/kg/h) usually maintain satisfactory anaesthesia.

Slightly higher rates of administration may be required for 10 to 20 minutes after induction of anaesthesia.

Repeat bolus injections:

As a guide, increments of 25 mg (2,5 mL) to 50 mg (5,0 mL) may be used.

Sedation during intensive care

To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that PROPOFOL MCT/LCT 1 % FRESENIUS should be given by continuous infusion, for up to 72 hours. The dose should be adjusted according to the depth of sedation required. Usually, satisfactory sedation is achieved with administration rates in the range of 0,3 mg/kg/h to 4,0 mg/kg/h. Rates of infusion greater than 4 mg/kg/h are not recommended.

PROPOFOL MCT/LCT 1 % FRESENIUS must not be used for sedation in intensive care of patients 16 years of age or younger.

Administration of PROPOFOL MCT/LCT 1 % FRESENIUS by a Target Controlled Infusion (TCI) system is not advised for sedation in the Intensive Care Unit.

Conscious sedation for surgical and diagnostic procedures *(see section 4.4)*

To provide sedation for surgical and diagnostic procedures rates of administration should be individualised and titrated to clinical response.

Most patients will require 0,5 mg/kg to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating PROPOFOL MCT/LCT 1 % FRESENIUS infusion to the desired level of sedation - most patients will require 1,5 mg/kg/h to 4,5 mg/kg/h. In addition to the infusion, bolus administration of 10 mg to 20 mg may be used if a rapid increase in the depth of sedation is required.

In patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

PROPOFOL MCT/LCT 1 % FRESENIUS must not be used for conscious sedation for diagnostic and surgical procedures in patients of 16 years of age or younger.

B. ELDERLY PATIENTS

In elderly patients the dose requirement for induction of anaesthesia with PROPOFOL MCT/LCT 1 % FRESENIUS is reduced. The reduction should consider the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response.

Where PROPOFOL MCT/LCT 1 % FRESENIUS is used for maintenance of anaesthesia or sedation the rate of infusion or "target concentration" should also be reduced. Patients of ASA Grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. CHILDREN

Induction of general anaesthesia

PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for use in children less than 3 years of age (see sections 4.3 and 4.4).

PROPOFOL MCT/LCT 1 % FRESENIUS should be given slowly until the clinical signs show the onset of anaesthesia.

The dosage should be adjusted for age and/or body weight.

Children over 8 years of age are likely to require approximately 2,5 mg/kg (0,25 mL/kg) of PROPOFOL MCT/LCT 1 % FRESENIUS for induction of anaesthesia. Between the ages of 3 and 8 years the dose requirement may be higher.

Lower doses are recommended for young patients at increased risk (ASA Grades 3 and 4).

Administration of PROPOFOL MCT/LCT 1 % FRESENIUS by a Target Controlled Infusion (TCI) system is not advised for induction of general anaesthesia in children.

Maintenance of general anaesthesia

PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for use in children less than 3 years of age (see section 4.3).

Administer PROPOFOL MCT/LCT 1 % FRESENIUS by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients. 9 mg/kg/h to 15 mg/kg/h (0,9 mL/kg/h to 1,5 mL/kg/h) usually achieves satisfactory anaesthesia.

Administration of PROPOFOL MCT/LCT 1 % FRESENIUS by a Target Controlled Infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

Sedation during intensive care

PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for sedation in children 16 years of age or younger, as safety and efficacy have not been demonstrated (see sections 4.3 and 4.4).

Conscious sedation for surgical and diagnostic procedures

PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for conscious sedation in children as safety and efficacy has not been demonstrated.

The duration of administration must not exceed 72 hours.

Method of administration

For intravenous use.

PROPOFOL MCT/LCT 1 % FRESENIUS and any infusion equipment containing PROPOFOL MCT/LCT 1 % FRESENIUS are for **single** administration in an **individual** patient. After use remaining solution of PROPOFOL MCT/LCT 1 % FRESENIUS must be discarded.

Containers should be shaken before use.

PROPOFOL MCT/LCT 1 % FRESENIUS should be inspected for particulate matter and discolouration before administration. Do not use if there is evidence of separation of the phases of the emulsion. Use only homogeneous preparations and undamaged containers.

General anaesthesia:

In accordance with established guidelines for other lipid emulsions a single infusion of PROPOFOL MCT/LCT 1 % FRESENIUS must not exceed 6 hours. The syringe or giving set and any unused portion of PROPOFOL MCT/LCT 1 % FRESENIUS or solution containing

PROPOFOL MCT/LCT 1 % FRESENIUS must be discarded at the end of the surgical procedure, or at 6 hours, whichever is the sooner, and replaced as appropriate.

Intensive care sedation:

Administration should commence promptly and must be completed within 12 hours after opening the ampoule or breaking the vial seal. The tubing and any unused portions of PROPOFOL MCT/LCT 1 % FRESENIUS must be discarded after 12 hours.

If PROPOFOL MCT/LCT 1 % FRESENIUS is transferred to another container prior to administration, the handling procedures for *"General anaesthesia*" (above) should be followed and the product should be discarded and administration lines changed after 6 hours.

When PROPOFOL MCT/LCT 1 % FRESENIUS is used undiluted to maintain anaesthesia, it is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

PROPOFOL MCT/LCT 1 % FRESENIUS can be diluted in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per mL) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation (see section 6.6).

The dilution may be used with a variety of infusion control techniques, but a giving set used alone will not avoid the risk of accidental, uncontrolled infusion of large volumes of diluted PROPOFOL MCT/LTC 1 % FRESENIUS. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be considered when deciding the maximum amount of PROPOFOL MCT/LCT 1 % FRESENIUS in the burette.

It is recommended that, when using diluted PROPOFOL MCT/LCT 1 % FRESENIUS, the volume of the diluent removed from the infusion bag during the dilution process is totally replaced in volume by PROPOFOL MCT/LCT 1 % FRESENIUS emulsion.

To reduce pain at the injection site, lidocaine (lignocaine) may be injected immediately before the use of PROPOFOL MCT/LCT 1 % FRESENIUS or PROPOFOL MCT/LCT 1 % FRESENIUS may be mixed, immediately before use, with preservative-free lidocaine (lignocaine) injection (20 parts of PROPOFOL MCT/LCT 1 % FRESENIUS with up to 1 part of 1 % lidocaine (lignocaine) injection solution) under controlled and validated aseptic conditions. The mixture must be administered within 6 hours of preparation (see section 6.6). Dilutions with lidocaine (lignocaine) solution must not be used in patients with hereditary acute porphyria.

Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of PROPOFOL MCT/LCT 1 % FRESENIUS.

4.3 Contraindications

- Known hypersensitivity to propofol or to any of the excipients of PROPOFOL MCT/LCT 1 % FRESENIUS (listed in section 6.1).
- PROPOFOL MCT/LCT 1 % FRESENIUS contains soya oil and should not be used in patients who are hypersensitive to peanuts or soya.
- PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for use in children less than 3 years of age.
- Sedation in children and adolescents 16 years of age and younger in intensive care (see section 4.4).

- Sedation of children of all ages with croup or epiglottitis receiving intensive care (see section 4.4).

4.4 Special warnings and precautions for use

PROPOFOL MCT/LCT 1 % FRESENIUS should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in intensive care).

Respiration will be depressed and must be monitored to ensure adequate gas exchange. Special care should be exercised when used with other respiratory depressants.

Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment and other resuscitative facilities should be readily available at all times. PROPOFOL MCT/LCT 1 % FRESENIUS should not be administered by the person conducting the diagnostic or surgical procedure.

A generalised systemic reaction which may be anaphylactic in nature (including angioedema, bronchospasm, erythema and hypotension) may occur following PROPOFOL MCT/LCT 1 % FRESENIUS administration - estimated as 1 in 15 000.

Abuse of and dependence on propofol, predominantly by healthcare professionals, have been reported. As with other general anaesthetics, the administration of PROPOFOL MCT/LCT 1 % FRESENIUS without airway care may result in fatal respiratory complications.

When PROPOFOL MCT/LCT 1 % FRESENIUS is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

When PROPOFOL MCT/LCT 1 % FRESENIUS is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of PROPOFOL MCT/LCT 1 % FRESENIUS. The use of propofol, as in PROPOFOL MCT/LCT 1 % FRESENIUS, may be associated with the development of a period of postoperative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

Propofol induced impairment is not generally detectable beyond 12 hours. The effects of propofol, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other medicines that may sedate (e.g., benzodiazepines, opiates, alcohol).

Interference with daily activities may continue for up to 24 hours and no legal/contractual decisions should be entered into for 24 hours after receiving anaesthetic/conscious sedation. Alcohol use should also be avoided for the same time period.

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When PROPOFOL MCT/LCT 1 % FRESENIUS is combined with centrally depressant medicines administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended

that PROPOFOL MCT/LCT 1 % FRESENIUS is administered following the analgesic and the dose should be carefully titrated to the patient's response (see section 4.5).

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other medicines.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of PROPOFOL MCT/LCT 1 % FRESENIUS during the period of anaesthetic maintenance.

Special patient groups

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia

Caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients.

Propofol clearance is blood flow dependent, therefore, concomitant administration of medicines which reduces cardiac output will also reduce propofol clearance.

The pharmacokinetics of propofol may be prolonged in people with chronic hepatic cirrhosis or chronic renal impairment. Recovery times may double as a result. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.

During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.

PROPOFOL MCT/LCT 1 % FRESENIUS should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.

Due to a higher dosage in patients with severe overweight the risk of haemodynamic effects on the cardiovascular system should be taken into consideration.

The risk of relative vagotonia may be increased because PROPOFOL MCT/LCT 1 % FRESENIUS lacks vagolytic activity. It has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic medicine before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate, or when PROPOFOL MCT/LCT 1 % FRESENIUS is used in conjunction with other medicines likely to cause a bradycardia. Routine premedication with anticholinergic medicines is not advised.

Epilepsy

When PROPOFOL MCT/LCT 1 % FRESENIUS is administered to an epileptic patient, there may be a risk of convulsion. PROPOFOL MCT/LCT 1 % FRESENIUS should therefore be used with caution in patients with epilepsy.

Delayed epileptiform attacks may occur even in non-epileptic patients, the delay period ranging from a few hours to several days.

Before anaesthesia of an epileptic patient, it should be checked that the patient has received antiepileptic treatment. Although several studies have demonstrated efficacy in treating status epilepticus, administration of PROPOFOL MCT/LCT 1 % FRESENIUS in epileptic patients may also increase the risk of seizure.

Use of PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended with electroconvulsive therapy.

Paediatric population

PROPOFOL MCT/LCT 1 % FRESENIUS is contraindicated in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

PROPOFOL MCT/LCT 1 % FRESENIUS is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes (see section 4.3).

PROPOFOL MCT/LCT 1 % FRESENIUS must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections, given doses in excess of those recommended for adults. Associated findings include metabolic acidosis, lipaemia, rhabdomyolosis, cardiac irregularities and renal failure.

Patients with disorders of fat metabolism

Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed to fat embolism and in other conditions where lipid emulsions must be used with caution. Lipids should be monitored in the Intensive Care Unit treatment after 3 days.

Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolic disorders, severe trauma including long-bone and multiple fractures, and sepsis.

Blood lipid levels should be monitored if PROPOFOL MCT/LCT 1 % FRESENIUS is administered to patients thought to be at particular risk of fat overload. Administration of PROPOFOL MCT/LCT 1 % FRESENIUS should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If patients receive parenteral nutrition, it is necessary to take account of the amount of lipid infusion as part of the PROPOFOL MCT/LCT 1 % FRESENIUS formulation (1,0 mL of PROPOFOL MCT/LCT 1 % FRESENIUS contains 0,1 g of fat).

Patients with high intracranial pressure

Special care and close monitoring should be exercised in patients with a high intracranial pressure and a low mean arterial pressure as there is a risk of a significant decrease of the intracerebral pressure.

Mitochondrial disease

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the “propofol infusion syndrome” may be similar.

Advisory statements concerning ICU management (Propofol infusion syndrome)

Use of propofol emulsion infusions (including PROPOFOL MCT/LCT 1 % FRESENIUS) for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death. Reports have been received of combinations of the following: metabolic acidosis, rhabdomyolysis, hyperkalaemia, hepatomegaly, renal failure, hyperlipidaemia, cardiac dysrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive cardiac failure usually unresponsive to inotropic supportive treatment (see section 4.8).

Combinations of these events have been referred to as the "propofol infusion syndrome". These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the ICU.

The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological substances - vasoconstrictors, steroids, inotropes and/or propofol (as in PROPOFOL MCT/LCT 1 % FRESENIUS, usually at dose rates greater than 4 mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue PROPOFOL MCT/LCT 1 % FRESENIUS when the above signs develop. All sedative and therapeutic medicines used in the ICU, should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intracranial pressure (ICP) should be given

appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Treating medical practitioners are reminded, if possible, not to exceed the dosage of 4 mg/kg/h.

Information on some of the ingredients

PROPOFOL MCT/LCT 1 % FRESENIUS contains soybean oil, which may cause severe allergic reactions. PROPOFOL MCT/LCT 1 % FRESENIUS should not be used in patients with an allergy to peanuts, eggs, or soya protein (see section 4.3).

PROPOFOL MCT/LCT 1 % FRESENIUS contains less than 1 mmol (23 mg) sodium per 100 mL, i.e. essentially “sodium- free”.

4.5 Interaction with other medicines and other forms of interaction

PROPOFOL MCT/LCT 1 % FRESENIUS has been used in association with spinal and epidural anaesthesia and with commonly used premedications, neuromuscular blocking medicines, inhalational medicines and analgesics; no pharmacological incompatibility has been encountered. Dosage adjustment may be necessary when used together with the above medicines, particularly the narcotics (e.g. morphine, meperidine and fentanyl), combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, droperidol etc.), supplementary analgesic medicines (e.g. nitrous oxide or opioids) and the potent inhalation medicines (e.g. isoflurane, enflurane and halothane).

Lower doses of PROPOFOL MCT/LCT 1 % FRESENIUS may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.

Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

The concurrent administration of other central nervous system (CNS) depressants such as premedications, inhalation medicines, analgesics, sedatives such as benzodiazepines, opiates, alcohol, may add to the sedative, anaesthetic and cardiorespiratory depressant effects of PROPOFOL MCT/LCT 1 % FRESENIUS (see section 4.4).

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmine.

Leukoencephalopathy has been reported with administration of lipid emulsions such as PROPOFOL MCT/LCT 1 % FRESENIUS in patients receiving ciclosporin.

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of PROPOFOL MCT/LCT 1 % FRESENIUS may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

PROPOFOL MCT/LCT 1 % FRESENIUS should not be used in pregnancy.

PROPOFOL MCT/LCT 1 % FRESENIUS crosses the placenta and can cause neonatal depression. PROPOFOL MCT/LCT 1 % FRESENIUS should not be used for obstetric

anaesthesia. PROPOFOL MCT/LCT 1 % FRESENIUS has been used, however, during termination of pregnancy in the first trimester.

Breastfeeding

PROPOFOL MCT/LCT 1 % FRESENIUS is excreted in small amounts into the milk. Therefore, mothers should not breastfeed for 24 hours after administration of PROPOFOL MCT/LCT 1 % FRESENIUS. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

After administration of PROPOFOL MCT/LCT 1 % FRESENIUS, the patient should be kept under observation for an appropriate period of time. The patient should be instructed not to drive, operate machinery, or work in potentially hazardous situations. The patient should not be allowed to go home unaccompanied and should be instructed to avoid consumption of alcohol.

Propofol induced impairment is not generally detectable beyond 12 hours (see section 4.4).

4.8 Undesirable effects

a. Summary of the safety profile

Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation.

The most frequently reported adverse reactions are pharmacologically predictable side effects of an anaesthetic/sedative medicine, such as hypotension. The nature, severity and incidence of

adverse events observed in patients receiving propofol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

b. Tabulated list of adverse reactions

SYSTEM ORGAN CLASS/ ADVERSE REACTION ***FREQUENCY***	
Immune system disorders:	
Less frequent:	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutritional disorders:	
Frequency not known[9]*:*	Metabolic acidosis[5], hyperkalaemia[5], hyperlipidaemia[5]
Psychiatric disorders:	
Frequency not known[9]:	Euphoric mood, sexual disinhibition, medicine abuse and dependence[8]
Nervous system disorders:	
Frequent:	Headache during recovery phase
Less frequent:	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery, vertigo, shivering and sensation of cold during recovery, postoperative unconsciousness
Frequency not known[9]	Involuntary movements
Cardiac disorders:	
Frequent:	Bradycardia[1] and tachycardia during induction

Less frequent: Pulmonary oedema

Frequency not known[9]*:* Cardiac dysrhythmia[5], cardiac failure[5,7]

Vascular disorders:

Frequent: Hypotension[2]

Less frequent: Thrombosis and phlebitis

Respiratory, thoracic and mediastinal disorders:

Frequent: Transient apnoea, coughing, singultus during induction

Frequency not known[9]*:* Respiratory depression (dose dependent)

Gastrointestinal disorders:

Frequent: Nausea and vomiting during recovery phase

Less frequent: Pancreatitis

Hepatobiliary disorders:

Frequency not known[9]: Hepatomegaly[5]

Musculoskeletal and connective tissue disorders:

Frequency not known[9]*:* Rhabdomyolysis[3,5]

Renal and urinary disorders:

Less frequent: Discolouration of urine following prolonged administration

Frequency not known[9]*:* Renal failure[5]

Reproductive system and breast disorders:

Frequency not known:	Priapism
General disorders and administration site conditions:	
Frequent:	Local pain on induction[4]
Less frequent:	Tissue necrosis[10] following accidental extravascular administration
Frequency not known[9]:	Local pain, swelling, following accidental extravascular administration
Investigations:	
Frequency not known[9]:	Brugada-type ECG[5,6]
Injury, poisoning and procedural complications:	
Less frequent:	Postoperative fever

(1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of PROPOFOL MCT/LCT 1 % FRESENIUS.

(3) Reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/h for ICU sedation.

(4) May be minimised by using the larger veins of the forearm and antecubital fossa. Local pain can also be minimised by the injection of lidocaine (lignocaine) immediately before the use of PROPOFOL MCT/LCT 1 % FRESENIUS (see section 4.2 - Method of administration).

(5) Combinations of these events, reported as “Propofol infusion syndrome”, may be seen in seriously ill patients who often have multiple risk factors for the development of the events (see section 4.4).

(6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.

(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

(8) Abuse of propofol and dependence on propofol, predominantly by healthcare professionals.

(9) Not known as it cannot be estimated from the available clinical trial data.

(10) Necrosis has been reported where tissue viability has been impaired.

Dystonia/dyskinesia have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patient's head and, if severe, use of plasma expanders and pressor substances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics; Other general anaesthetics

ATC-Code: N01AX10

Category and class: A 2.1 Anaesthetics

Mechanism of action

Propofol (2,6-di-isopropylphenol) is a short-acting sedative hypnotic with a rapid onset of action of approximately 30 seconds. The mechanism of action is poorly understood.

Pharmacodynamic effects

Falls in mean arterial blood pressure and changes in heartrate are observed when propofol is administered.

Ventilatory depression can occur following administration of propofol.

Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism.

Clinical efficacy and safety

Recovery from anaesthesia is usually rapid and clear-headed.

Propofol has an anti-emetic effect.

Propofol, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 Pharmacokinetic properties

Absorption

The decline in propofol concentrations following the termination of an infusion can be described by a 3-compartment open model.

The first phase is characterised by a rapid distribution (half-life: 2 to 4 minutes) followed by rapid elimination (half-life: 30 to 60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Distribution/Biotransformation/Elimination

Propofol is bound to plasma proteins for 98 %.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance: 1,5 – 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

The pharmacokinetics are linear over the recommended range of infusion rates of propofol.

Under the usual maintenance regimens, significant accumulation of propofol does not occur.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined

Medium-chain triglycerides

Purified egg phosphatides

Glycerol

Oleic acid

Sodium hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

PROPOFOL MCT/LCT 1 % FRESENIUS must not be mixed with other solutions for infusion or injection except those mentioned in section 6.6.

Muscle relaxants like atracurium and mivacurium should not be given through the same intravenous line as PROPOFOL MCT/LCT 1 % FRESENIUS without prior flushing.

6.3 Shelf life

Shelf life in original package before opening: 24 months.

Shelf life after first opening: PROPOFOL MCT/LCT 1 % FRESENIUS must be used immediately after first opening.

Shelf life after dilution: PROPOFOL MCT/LTC 1 % FRESENIUS must be used immediately after dilution. The administration should be completed within 6 hours after dilution.

6.4 Special precautions for storage

Store at or below 30 °C.

Do not freeze.

6.5 Nature and contents of container

5 clear, colourless glass ampoules with 20 mL emulsion for injection or infusion

5 and 10 clear, colourless glass vials with 20 mL emulsion for injection or infusion, sealed with a grey rubber stopper

1, 10 and 15 clear, colourless glass infusion bottles with 50 mL emulsion for injection or infusion, sealed with a grey rubber stopper

1, 10 and 15 clear, colourless glass infusion bottles with 100 mL emulsion for injection or infusion, sealed with a grey rubber stopper

The ampoules/vials/infusion bottles are packed in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When PROPOFOL MCT/LCT 1 % FRESENIUS is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay.

Asepsis must be maintained for both PROPOFOL MCT/LCT 1 % FRESENIUS and infusion equipment throughout the infusion period. Co-administration of other medicines or fluids added

to the PROPOFOL MCT/LCT 1 % FRESENIUS infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve.

PROPOFOL MCT/LCT 1 % FRESENIUS must not be administered via a microbiological filter.

PROPOFOL MCT/LCT 1 % FRESENIUS must not be mixed prior to administration with injection or infusion solutions other than glucose (dextrose) 50 mg/mL (5 %) solution for injection, sodium chloride 9 mg/mL (0,9 %) solution for injection, preservative free lidocaine (lignocaine) 10 mg/mL (1 %) solution for injection or alfentanil injection.

The maximum dilution must not exceed 1 part of PROPOFOL MCT/LCT 1 % FRESENIUS with 4 parts of glucose 50 mg/mL (5 %) solution for injection or sodium chloride 9 mg/mL (0,9 %) solution for injection (minimum propofol concentration: 2 mg/mL). The mixture must be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 6 hours after preparation (see also section 4.2).

Any unused emulsion must be discarded. PROPOFOL MCT/LCT 1 % FRESENIUS contains no antimicrobial preservatives and the vehicle supports growth of microorganisms.

Final propofol concentration must not be below 2 mg/mL.

Co-administration of a glucose 50 mg/mL (5 %) solution for injection or sodium chloride 9 mg/mL (0,9 %) solution for injection or sodium chloride 1,8 mg/mL (0,18 %) solution for injection and glucose 40 mg/mL (4 %) solution for injection with PROPOFOL MCT/LCT 1% FRESENIUS is permitted via a Y-piece connector close to the injection site.

Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

Administration of PROPOFOL MCT/LCT 1 % FRESENIUS by Target Controlled Infusion (TCI) in adults:

PROPOFOL MCT/LCT 1 % FRESENIUS may also be used by Target Controlled Infusion (TCI). Due to the different algorithms available on the market for dosage recommendations, please refer to the instructions for use leaflet of the device manufacturer. Administration of PROPOFOL MCT/LCT 1 % FRESENIUS via a TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in children or in ICU sedation or sedation for surgical and diagnostic procedures.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7

Midrand, 1685

South Africa

8. REGISTRATION NUMBERS

PROPOFOL MCT/LCT 1 % (20 mL) FRESENIUS: 41/2.1/1121

PROPOFOL MCT/LCT 1 % (50 mL) FRESENIUS: 41/2.1/1122

PROPOFOL MCT/LCT 1% (100 mL) FRESENIUS: 41/2.1/1123

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 01 March 2013

10. DATE OF REVISION OF THE TEXT

17 July 2024