SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propofol 1% MCT Fresenius

2. QUALITIATIVE AND QUANTITATIVE COPOSITION

Each ml emulsion contains 10 mg propofol.
Each 20 ml ampoule contains 200 mg propofol.
Each 20 ml vial contains 200 mg propofol.
Each 50 ml vial contains 500 mg propofol.
Each 100 ml vial contains 1000 mg propofol.

Excipients with known effect:
soya-bean oil
Sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion.
Propofol 1% MCT Freseniusis a white, oil-in-water emulsion for intravenous administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 1% MCT Fresenius is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children > 1 month
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 1 month
- sedation of ventilated patients > 16 years of age in the intensive care unit

4.2 Posology and method of administration

Propofol 1% MCT Fresenius must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care.
Circulatory and respiratory functions should be constantly monitored (e.g. ECG,

pulse oxymetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.

For sedation during surgical and diagnostic procedures Propofol 1% MCT Fresenius should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Propofol 1% MCT Fresenius should be individualised based on the response of the patient and premedications used.

Supplementary analgesic agents are generally required in addition to Propofol 1% MCT Fresenius

Posology

General anaesthesia in adults

Induction of anaesthesia:

For induction of anaesthesia Propofol 1% MCT Fresenius should be titrated (approximately 20 - 40 mg propofol every 10 seconds) against the response of the patient until clinical signs show the onset of anaesthesia.

Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg propofol/kg bodyweight.

In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Propofol 1% MCT Fresenius may be reduced to a minimum of 1 mg propofol/kg bodyweight. Lower rates of administration of Propofol 1% MCT Fresenius should be used (approximately 2 ml of the 10mg/ml emulsion (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 1% MCT Fresenius either by continuous infusion or repeat bolus injections.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg bodyweight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg bodyweight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

In elderly patients, patients in unstable general conditions, patients with impaired

cardiac function or hypovolaemic patients and patients of ASA grades III and IV the dosage of Propofol 1% MCT Fresenius may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

For maintenance of anaesthesia with Propofol 1% MCT Fresenius using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 – 5 ml Propofol 1% MCT Fresenius) should be given according to clinical requirements.

Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiopulmonary depression.

General anaesthesia in children over 1 month of age

Induction of anaesthesia:

For induction of anaesthesia Propofol 1% MCT Fresenius should be titrated slowly until clinical signs show the onset of anaesthesia.
The dose should be adjusted according to age and/or bodyweight. Most patients over 8 years of age require approximately 2.5 mg/kg bodyweight Propofol 1% MCT Fresenius for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5 – 4 mg/kg bodyweight).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering Propofol 1% MCT Fresenius by infusion or repeated bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9-15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA III and IV patients lower doses are recommended (see also section 4.4).

Sedation for diagnostic and surgical procedures in adult patients

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 - 1 mg propofol/kg bodyweight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% MCT Fresenius to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg bodyweight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg propofol (1 – 2 ml Propofol 1% MCT Fresenius) if a rapid increase of the depth of sedation is required.

In patients older than 55 years and in patients of ASA grades III and IV lower doses

of Propofol 1% MCT Fresenius may be required and the rate of administration may need to be reduced.

Sedation for diagnostic and surgical procedures in children over 1 month of age

Doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1 – 2 mg/kg bodyweight propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% MCT Fresenius infusion to the desired level of sedation. Most patients require 1.5 - 9 mg/kg/h propofol. With Propofol 1% MCT Fresenius the infusion may be supplemented by bolus administration of up to 1 mg/kg bodyweight if a rapid increase of depth of sedation is required.

In ASA III and IV patients lower doses may be required.

Sedation in patients over 16 years of age adults during intensive care

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol 1% MCT Fresenius should be given by continuous infusion. 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 to 4.0 mg propofol/kg bodyweight/h. Rates of infusion greater than 4.0 mg propofol/kg bodyweight/h are not recommended (see section 4.4).

Administration of propofol by a target controlled infusion (TCI) system is not advised for sedation in the intensive care unit (ICU).

Duration of administration

The duration of administration must not exceed 7 days.

Method of administration

For intravenous use.
For single use only. Any unused emulsion must be discarded.

Containers should be shaken before use.
If two layers can be seen after shaking the emulsion should not be used.
Use only homogeneous preparations and undamaged containers.

Propofol 1% MCT Fresenius can be used for infusion undiluted or diluted (for dilution see section 6.6).

When Propofol 1% MCT Fresenius is infused, it is recommended that equipment

such as burettes, drop counter, syringe pumps (including TCI systems) or volumetric infusion pumps should always be used to control infusion rates.

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.

Propofol 1% MCT Fresenius is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of micro-organisms.
The emulsion 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 1% MCT Fresenius and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Propofol 1% MCT Fresenius infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve. For instructions on co-administration of the medicinal product, see section 6.6.

Propofol 1% MCT Fresenius must not be administered via a microbiological filter.

Propofol 1% MCT Fresenius and any infusion equipment containing Propofol 1% MCT Fresenius are for single administration in an individual patient. After use remaining solution of Propofol 1% MCT Fresenius has to be discarded.

Infusion of undiluted Propofol 1% (10 mg/1 ml) MCT Fresenius:

As usual for fat emulsions, the infusion of Propofol 1% MCT Fresenius via one infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Propofol 1% MCT Fresenius must be discarded or replaced if necessary.

Infusion of diluted Propofol 1% MCT Fresenius:

For administering infusion of diluted Propofol 1% MCT Fresenius, burettes, drop counters or volumetric infusion pumps should always be used to control infusion rates and to avoid the risk of accidentally uncontrolled infusion of large volumes of diluted Propofol 1% MCT Fresenius. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

The maximum dilution must not exceed 1 part of Propofol 1% (10 mg/1 ml) MCT Fresenius with 4 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration 2 mg propofol per ml). The mixture should be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 6 hours after preparation.

Propofol 1% (10 mg/1 ml) MCT Fresenius must not be mixed with other solutions for infusion or injection. However, co-administration of a 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 0.18% w/v sodium chloride and 4% w/v glucose solution with Propofol 1% (10 mg/1 ml) MCT Fresenius is permitted via a Y-piece connector close to the injection site.

To reduce pain on the injection site, lidocaine may be injected immediately before the use of Propofol 1% MCT Fresenius (see section 4.4). Alternatively, Propofol 1% MCT Fresenius may be mixed, immediately for use, with preservative free lidocaine injection (20 parts of Propofol 1% MCT Fresenius with up to 1 part of 1% lidocaine injection solution) under controlled and validated aseptical conditions. The mixture has to be administered within 6 hours after preparation.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Propofol 1% MCT Fresenius.

If Propofol 1% MCT Fresenius is injected into a vein by electric pumps, appropriate compatibility should be ensured.

Target Controlled Infusion – Administration of Propofol 1% MCT Fresenius by pumps (for 20 ml plastic and 50 ml plastic syringe only):

Administration of Propofol 1% MCT Fresenius by a Target Controlled Infusion system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures or in children.

Propofol 1% MCT Fresenius may be administered by a Target Controlled Infusion system incorporating appropriate Target Controlled Infusion software. Users must be familiar with the infusion pump users' manual, and with the administration of Propofol 1% MCT Fresenius by Target Controlled Infusion.

The system allows the anaesthetist or intensivist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) plasma and/or effect-side concentrations of propofol.

Different modalities of the various pump systems should be considered i.e. the Target Controlled Infusion system might assume that the initial blood propofol concentration in the patient is zero. Therefore, in patients who have received prior propofol, there may be a need to select a lower initial target concentration when commencing Target Controlled Infusion. Similarly, the immediate recommencement of Target Controlled Infusion is not recommended if the pump has been switched off.

Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both

premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

Induction and Maintenance of General Anaesthesia during target controlled infusion

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4 – 8 microgram/ml. An initial target of patients an initial target of 6 microgram/ml is advised. Induction time with these 4 microgram/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 microgram/ml is advised. Induction time with these targets is generally within the range of 60–120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration can then be increased in steps of 0.5 – 1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3–6 microgram/ml usually maintain satisfactory anaesthesia.

The predicted propofol concentration on waking is generally in the region of 1.0 – 2.0 microgram/ml and will be influenced by the amount of analgesia given during maintenance.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Propofol 1% MCT Fresenius contains soya bean oil and should not be used in patients who are hypersensitive to peanut or soya.
Propofol 1% MCT Fresenius must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

4.4 Special warnings and precautions for use

Propofol 1% MCT Fresenius should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care).

Patients should be constantly monitored and facilities for maintenance of a patient

airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Propofol 1% MCT Fresenius should not be administered by the person conducting the diagnostic or surgical procedure.

Abuse of, and dependence on Propofol 1% MCT Fresenius ,predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Propofol 1% MCT Fresenius without airway care may result in fatal respiratory complications.

When Propofol 1% MCT 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.

As with other sedative agents, when Propofol 1% MCT 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 1% MCT Fresenius. Very rarely the use of Propofol 1% MCT 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 1% MCT Fresenius induced impairment is not generally detectable beyond 12 hours. The effects of Propofol 1% MCT Fresenius,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 agents that may sedate (e.g., benzodiazepines, opiates, alcohol)

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. Propofol 1% MCT Fresenius clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Propofol 1% MCT Fresenius clearance.

Propofol 1% MCT Fresenius lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. 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 predominate, or when Propofol 1% MCT Fresenius is used in conjunction with other agents likely to cause a bradycardia.

As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of Propofol 1% MCT Fresenius.

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

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects.

When Propofol 1% MCT Fresenius is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that Propofol 1% MCT 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 agents.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Propofol 1% MCT Fresenius during the period of anaesthetic maintenance.

When Propofol 1% MCT Fresenius is administered to an epileptic patient, there may be a risk of convulsion.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously (see section 4.2).

Use is not recommended with electroconvulsive treatment. As with other anaesthetics, sexual disinhibition may occur during recovery.

The benefits and risks of the proposed procedure should be considered prior to proceeding with repeated or prolonged use (>3 hours) of propofol in young children (<3 years) and in pregnant women as there have been reports of neurotoxicity in preclinical studies, see Section 5.3.

Paediatric population

The use of Propofol 1% MCT Fresenius is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) 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 2% MCT Fresenius is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes. Propofol 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).

Advisory statements concerning Intensive Care Unit management

Use of propofol emulsion infusions 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 arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. 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 intensive care unit. 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 agents - vasoconstrictors, steroids, inotropes and/or Propofol 1% MCT Fresenius (usually at dose rates greater than 4mg/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 when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU), should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.
Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation; 1.0 mL of Propofol 1% MCT Fresenius contains approximately 0.1 g of fat.
This medicinal product contains less than 1 mmol (23 mg) sodium per 100 ml, i.e. essentially “sodium- free”.

Additional Precautions

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.
Propofol 1% MCT Fresenius contains no antimicrobial preservatives

and supports growth of micro-organisms.

EDTA chelates metal ions, including zinc, and reduces microbial growth rates. The need for supplemental zinc should be considered during prolonged administration of Propofol 1% MCT Fresenius , particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

When Propofol 1% MCT 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 1% MCT Fresenius and infusion equipment throughout the infusion period. Any infusion fluids added to the Propofol 1% MCT Fresenius line must be administered close to the cannula site. Propofol 1% MCT Fresenius must not be administered via a microbiological filter.

Propofol 1% MCT Fresenius and any syringe containing Propofol 1% MCT Fresenius are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of propofol must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner; both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

4.5 Interaction with other medicinal productsand other forms of interaction

Propofol 1% MCT Fresenius has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Propofol 1% MCT Fresenius may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques. Profound hypotension has been reported following anaesthetic with propofol in patients treated with rifampicin.

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of Propofol 1% MCT Fresenius (see Section 4.4).

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Propofol 1% MCT Fresenius during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Propofol 1% MCT Fresenius should not be given to pregnant women except when absolutely necessary. Propofol 1% MCT Fresenius can, however, be used during an induced abortion.

Obstetrics

Propofol 1% MCT Fresenius crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

Breast-feeding

Studies of breast-feeding mothers showed that small quantities of Propofol 1% MCT Fresenius are excreted in human milk. Women should therefore not breast-feed for 24 hours after administration of Propofol 1% MCT Fresenius. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and use machines

Propofol 1% MCT Fresenius has moderate influence on the 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.

Propofol 1% MCT Fresenius induced impairment is not generally detectable beyond 12 hours (Section 4.4).

4.8 Undesirable effects

General

Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving Propofol 1% MCT Fresenius may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.
The following definitions of frequencies are used: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table of Adverse Drug Reactions

System OrganClass	Frequency	Undesirable Effects
Immune systemdisorders	Very rare	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutrition disorders	Not known [9]	Metabolic acidosis[5], hyperkalaemia [5], hyperlipidaemia [5]
Psychiatric disorders	Not known [9]	Euphoric mood. Drug abuse and drug dependence [8]

Nervous system disorders	Common	Headache during recovery phase
	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare	Postoperative unconsciousness
	Not known [9]	Involuntary movements
Cardiac disorders	Common	Bradycardia [1]
	Very rare	Pulmonary oedema
	Not known [9]	Cardiac arrhythmia [5], cardiac failure [5], [7]
Vascular disorders	Common	Hypotension [2]
	Uncommon	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Common	Transient apnoea during induction
	Not known [9]	Respiratory depression (dose dependent)
Gastrointestinal disorders	Common	Nausea and vomiting during recovery phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known [9]	Hepatomegaly [5]
Musculoskeletal and connective tissue disorders	Not known [9]	Rhabdomyolysis [3], [5]
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Not known [9]	Renal failure [5]
Reproductive system and breast disorders	Very rare	Sexual disinhibition
	Not known	Priapism
General disorders and administration site conditions	Very common	Local pain on induction [4]
	Very rare	Tissue necrosis [10] following accidental extravascular administration
	Not known [9]	Local pain, swelling, following accidental extravascular administration
Investigations	Not known [9]	Brugada type ECG [5], [6]
Injury, poisoning and procedural complications	Very rare	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 1% MCT Fresenius.
(3) Very rare reports of rhabdomyolysis have been received where Propofol 1% MCT Fresenius has been given at doses greater than 4 mg/kg/hr for ICU sedation.
(4) May be minimised by using the larger veins of the forearm and antecubital fossa. With Propofol 1% MCT Fresenius local pain can also be minimised by the co-administration of lidocaine.
(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 and drug dependence on propofol, predominantly by health care 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.

Local

The local pain which may occur during the induction phase of Propofol 1% MCT Fresenius anaesthesia can be minimised by the co- administration of lidocaine (see "Dosage and Administration") and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

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 agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics
ATC code: N01AX10

Mechanism of action

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors.

Pharmacodynamic properties

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Propofol 1% MCT Fresenius is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of Propofol 1% MCT Fresenius, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

Propofol 1% MCT Fresenius reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Clinical efficacy and safety

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

In general, there is less post-operative nausea and vomiting following anaesthesia with Propofol 1% MCT Fresenius than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol. Propofol 1% MCT Fresenius, at the concentrations likely to occur clinically, does not

inhibit the synthesis of adrenocortical hormones.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption

When Propofol 1% MCT Fresenius is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate.

Distribution

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5–2 litres/minute).

Elimination

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2–4 minutes), rapid elimination (half-life 30–60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

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.

After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates <1 month old (n=25) (20 ml/ kg/min) compared to older children (n= 36, age range 4 months–7 years). Additionally inter-individual variability was considerable in neonates (range 3.7–78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4–24 months) (n=8), 38.7 ml/min/kg (11–43 months) (n=6), 48 ml/min/kg (1–3 years)(n=12), 28.2 ml/min/kg (4–7 years)(n=10) as compared with

23.6 ml/min/kg in adults (n=6).

Linearity

The pharmacokinetics are linear over the recommended range of infusion rates of Propofol 1% MCT Fresenius.

5.3 Preclinical 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. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In neonatal primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anaesthesia in young children less than 3 years of age and pregnant women who require procedures against the potential risks suggested by the preclinical data.

Propofol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya bean oil
Medium Chain Triglycerides (MCT)
Glycerol anhydrous
Purified egg phospholipids
Oleic acid
Sodium Hydroxide
Water For Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

The neuromuscular blocking agent, atracurium, should not be given through the same intravenous line as Propofol 1% MCT Fresenius without prior flushing.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution

The mixture should be prepared aseptically immediately prior to administration and must be administered within 6 hours after preparation.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Glass ampoules: 5 x 20 ml

Glass vials: 1 x 20 ml, 5 x 20 ml, 10 x 20 ml

Glass bottles (Vial): 1 x 50 ml, 10 x 50, 15 x 50 ml, 1 x 100 ml, 10 x 100 ml, 15 x 100 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling In-use precautions

Containers must be shaken before use.
For single use. Any unused emultion must be discarded. After opening the product must be used immediately.
The mixture may be mixed with 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 1% preservative free lidocaine injection solution.

7. MANUFACTURER

Fresenius Kabi Deutschland GMBH

D-61346 Bad Homburg V.D.H., Germany

8. LICENSE HOLDER

Cure Medical & Technical Supply
6 Hashiloach St., POB 3340 Petach-Tikva

9. REGISTRATION NUMBERS

156-46-34397-00
156-46-34397-01
156-46-34397-02

Revised in April 2021 according to MOHs guidelines