FRESENIUS KABI

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propofol 2% (20 mg/1 ml) MCT Fresenius emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion contains 20 mg propofol.

Each 50 ml vial contains 1000 mg propofol.

Excipients:
1 ml emulsion contains:

soya-bean oil, refined	50 mg
sodium	max. 0,06 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion
White oil-in-water emulsion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 2% (20 mg/1 ml) MCT Fresenius is a short-acting intravenous general anaesthetic agent for

- induction and maintenance of general anaesthesia
- sedation of artificially ventilated patients in the Intensive Care Unit (ICU)

4.2 Posology and method of administration

Propofol 2% (20 mg/1 ml) 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.

The dose of Propofol 2% (20 mg/1 ml) MCT Fresenius emulsion should be individualised based on the response of the patient and premedications used.

Supplementary analgesic agents are generally required in addition to Propofol 2% (20 mg/1 ml) MCT Fresenius.

Posology

General anaesthesia in adults:

Induction of anaesthesia:

For induction of anaesthesia Propofol 2% (20 mg/1 ml) 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 body weight.

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 2% (20 mg/1 ml) MCT Fresenius may be reduced to a minimum of 1 mg propofol/kg body weight. Lower rates of administration of Propofol 2% (20 mg/1 ml) MCT Fresenius should be used (approximately 1 ml (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 2% (20 mg/1 ml) MCT Fresenius by continuous infusion.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg body weight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg body weight/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 2% (20 mg/1 ml) MCT Fresenius may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

General anaesthesia in children over 3 years of age:

Propofol 2% (20 mg/1 ml) MCT Fresenius is not advised for general anaesthesia in children between 1 month and 3 years of age since the 2% strength is difficult to be titrated in small children due to the extremely small volumes needed. The use of Propofol 1% (10 mg/1 ml) MCT Fresenius should be considered in children between 1 month and 3 years of age if a dose less than e.g. 100 mg/h is expected.
Propofol (both 1% and 2%) is not advised in children younger than 1 month of age.

Induction of anaesthesia:

When used to induce anaesthesia, it is recommended that Propofol 2% (20 mg/1 ml) MCT Fresenius should be titrated slowly until the clinical signs show the onset of anaesthesia.

The dose should be adjusted for age and/or body weight.
Children over 8 years of age are likely to require approximately 2.5 mg propofol/kg body weight for induction of anaesthesia. Under this age the dose requirement may be higher. The initial dose should be 3 mg propofol/kg body weight. If necessary, additional doses in steps of 1 mg propofol/kg body weight can be administered.

Lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Administration of propofol by a Target Controlled Infusion (TCI) system is not advised for induction of general anaesthesia in children.

Maintenance of anaesthesia:

For maintenance of anaesthesia using continuous infusion doses of 9 to 15 mg propofol/kg body weight/h should be given.

There is no data on maintenance of anaesthesia with repeated injections of propofol in children.

Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia.

Administration of propofol by a Target Controlled Infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

Sedation in adults during intensive care:

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol 2% (20 mg/1 ml) 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 body weight/h. Rates of infusion greater than 4.0 mg propofol/kg body weight/h are not recommended (see section 4.4 Special warnings and precautions for use).

Propofol 2% (20 mg/1 ml) MCT Fresenius must not be used for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications).

Administration of Propofol 2% (20 mg/1 ml) MCT Fresenius by a Target Controlled Infusion (TCI) system is not advised for sedation in the Intensive Care Unit.

Method of administration

For intravenous use.

Propofol 2% (20 mg/1 ml) MCT Fresenius is administered undiluted intravenously by ~~i~~continuous infusion. Propofol 2% (20 mg/1 ml) MCT Fresenius should not be given by repeat bolus injection for maintenance of anaesthesia.

When Propofol 2% (20 mg/1 ml) MCT Fresenius is infused, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

Containers should be shaken before use.
Use only homogeneous preparations and undamaged containers.

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

Propofol 2% (20 mg/1 ml) MCT Fresenius is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of microorganisms.

The emulsion must be drawn aseptically into a sterile syringe or giving set immediately after breaking the vial seal. Administration must commence without delay.

Asepsis must be maintained for both Propofol 2% (20 mg/1 ml) MCT Fresenius and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Propofol 2% (20 mg/1 ml) MCT Fresenius infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve.

Propofol 2% (20 mg/1 ml) MCT Fresenius must not be mixed with other solutions for infusion or injection. But 5% w/v glucose solution, 0.9% w/v sodium chloride solution or 0.18% w/v sodium chloride and 4% w/v glucose solution may be administered via suitable appendages at the cannula site.

Propofol 2% (20 mg/1 ml) MCT Fresenius must not be administered via a microbiological filter.

Propofol 2% (20 mg/1 ml) MCT Fresenius and any infusion equipment containing Propofol 2% (20 mg/1 ml) MCT Fresenius are for **single** administration in an **individual** patient. After use remaining solution of Propofol 2% (20 mg/1 ml) MCT Fresenius has to be discarded.

As usual for fat emulsions, the infusion of Propofol 2% (20 mg/1 ml) MCT Fresenius via **one** infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Propofol 2% (20 mg/1 ml) MCT Fresenius must be discarded or replaced if necessary.

To reduce pain on the injection site, Propofol 2% (20 mg/1 ml) MCT Fresenius should be administered in a larger vein or lidocaine injection solution may be administered before induction of anaesthesia with Propofol 2% (20 mg/1 ml) MCT Fresenius.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Propofol 2% (20 mg/1 ml) MCT Fresenius.

Duration of administration

The duration of administration must not exceed 7 days.

4.3 Contraindications

Propofol 2% (20 mg/1 ml) MCT Fresenius must not be used

- in patients with a known hypersensitivity to propofol, soya. peanut or to any of the excipients of the emulsion

- in patients who are allergic to soya or peanut

- for sedation in children and adolescents 16 years of age and younger (see section 4.4 Special warnings and precautions for use)

4.4 Special warning and precautions for use

In patients with cardiac, respiratory, renal or hepatic impairment or in elderly, debilitated, hypovolaemic or epileptic patients or patients with disorders of consciousness Propofol 2% (20 mg/1 ml) MCT Fresenius should be administered with caution and a reduced administration rate (see section 4.2 Posology and method of administration).

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of Propofol 2% (20 mg/1 ml) MCT Fresenius.

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

Propofol 2% (20 mg/1 ml) MCT Fresenius should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.
The risk of relative vagotonia may be increased because propofol lacks vagolytic activity. It 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 2% (20 mg/1 ml) MCT Fresenius is used in conjunction with other agents likely to cause a bradycardia.

Use of Propofol 2% (20 mg/1 ml) MCT is not recommended with electroconvulsive therapy.

Special care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used with caution. If patients receive parenteral nutrition it is necessary to take account of the amount of lipid infusion as part of the Propofol 2% (20 mg/1 ml) MCT Fresenius formulation: 1.0 ml Propofol 2% (20 mg/1 ml) MCT Fresenius contains 0.1 gram of fat.

Lipids should be monitored in the Intensive Care Unit treatment after 3 days.

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

Special care should be recognised 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 perfusion pressure.

To reduce pain on the injection site during induction of anaesthesia with Propofol 2% (20 mg/1 ml) MCT Fresenius, lidocaine can be injected prior to the propofol emulsion.

Dilutions with lidocaine solution must not be used in patients with hereditary acute porphyria.

Propofol 2% (20 mg/1 ml) MCT Fresenius is not advised for general anaesthesia in children younger than 3 years of age since the 2% strength is difficult to be titrated in small children due to the extremely small volumes needed. The use of Propofol 1% (10 mg/1 ml) MCT Fresenius should be considered in children between 1 month and 3 years of age if a dose less than e.g. 100 mg/h is expected. Propofol is not advised for general anaesthesia in children younger than 1 month of age.
In any case, special care should be exercised when propofol is used for anaesthesia in infants and children up to 3 years of age, although currently available data do not suggest significant differences in terms of safety compared with children older than 3 years.

The safety and efficacy of propofol for (background) sedation in children and adolescents younger than 16 years of age have not been demonstrated.

Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit. Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac

failure (in some cases with fatal outcome) in adults who were treated for more than 58 hours with dosages in excess of 5 mg propofol/kg body weight/h. This exceeds the maximum dosage of 4 mg propofol/kg body weight/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with increased intracranial pressure (ICP). The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
Treating physicians are reminded if possible not to exceed the dosage of 4 mg propofol/kg body weight/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the propofol dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

In isolated cases there may be a phase of postoperative unconsciousness that may be accompanied by an increased muscle tone. The occurrence of such an event is not related to whether the patient was awake or not. Although consciousness returns spontaneously, unconscious patients should be kept under close observation.

Full recovery from general anaesthesia should be confirmed prior to discharge.

This medicinal product contains less than 1 mmol (23 mg) sodium per 100 ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Propofol 2% (20 mg/1 ml) MCT Fresenius can be used in combination with other medicinal products for anaesthesia (premedications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics). Severe interactions with these medicinal products have been reported. Some of these centrally acting medicinal products may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Propofol 2% (20 mg/1 ml) MCT Fresenius.

Lower doses may be required when general anaesthesia is carried out in conjunction with regional anaesthesia.

Concomitant use of benzodiazepines, parasympatholytic agents or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.
After additional premedication with opioids, the sedative effects of propofol may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea.

It should be taken into consideration that concomitant use of propofol and medicinal products for premedication, inhalation agents, or analgesic agents may potentiate anaesthesia and cardiovascular side effects.

Concomitant use of central nervous system depressants (e.g. alcohol, general anaesthetics, narcotic analgesics) will result in intensification of their sedative effects. When Propofol 2% (20 mg/1 ml) MCT Fresenius is combined with centrally depressant agents administered parenterally, severe respiratory and cardiovascular depression may occur.
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 neostigmin.

Leucoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving cyclosporine.

4.6 Pregnancy and lactation

The safety of propofol during pregnancy has not been established. Therefore, propofol should not be used in pregnant women unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression (see section 5.3). High doses (more than 2.5 mg propofol/kg body weight for induction or 6 mg propofol/kg body weight/h for maintenance of anaesthesia) should be avoided.

Studies in breast-feeding women showed that propofol is excreted in small amounts into the milk. Therefore, mothers should stop breast-feeding and discard breast milk for 24 hours after administration of propofol.

4.7 Effects on ability to drive and use machines

After administration of Propofol 2% (20 mg/1 ml) MCT 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.

4.8 Undesirable effects

Commonly observed side effects of propofol are hypotension and respiratory depression. These effects depend on the propofol dose administered but also on the type of premedication and other concomitant medication.

In this section undesirable effects are defined as follows:
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); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:

Rare:
Clinical features of anaphylaxis, which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Metabolism and nutrition disorders:

Common: Hypertriglyceridemia.

Psychiatric disorders:

Rare:
Euphoria and sexual disinhibition during the recovery period.

Nervous system disorders:

Common:
During induction of anaesthesia spontaneous movements and myocloni, minimal excitation.

Rare:
Headache, vertigo, shivering and sensations of cold during the recovery period.
Epileptiform movements including convulsions and opisthotonus.

Very rare:
Delayed epileptiform attacks, the delay period ranging from a few hours to several days.
Risk of convulsions in epileptic patients after administration of propofol.
Cases of postoperative unconsciousness (see section 4.4 Special warnings and precautions for use).

Cardiac disorders / Vascular disorders:

Common:
During induction of anaesthesia, hypotension, bradycardia, tachycardia, hot flushes.

Uncommon:
Marked hypotension. This may require a lowering of the administration rate of Propofol 2% (20 mg/1 ml) MCT Fresenius and/or fluid replacement therapy, if necessary vasoconstrictive medicinal products. Account should be taken of the possibility of a severe drop in blood pressure in patients with impaired coronary or cerebral perfusion or those with hypovolaemia.
Bradycardia during general anaesthesia with progressive severity (asystole). The intravenous administration of an anticholinergic medicinal product prior to

induction or during maintenance of anaesthesia should be considered (see also section 4.4. Special warnings and precautions for use).

Rare:
Arrhythmia during the recovery period.
Thrombosis and phlebitis.

Respiratory, thoracic and mediastinal disorders:

Common:
During induction of anaesthesia hyperventilation, transient apnoea, coughing, singultus.

Uncommon:
Coughing during maintenance of anaesthesia.

Rare:
Coughing during the recovery period.

Very rare:
Pulmonary oedema.

Gastrointestinal disorders:

Rare:
Nausea or vomiting during the recovery period.

Very rare:
Pancreatitis has been reported after administration of propofol. A causal relationship, however, could not be established.

Skin and subcutaneous tissue disorders:

Very rare:
Severe tissue responses after accidental paravenous application.

Renal and urinary disorders:

Rare:
Cases of discoloration of urine following prolonged administration of propofol.

General disorders and administration site conditions:

Very common:
Local pain occurring during the initial injection. Prophylaxis or treatment see below.

The local pain which may occur during the initial injection of Propofol 2% (20 mg/1 ml) MCT Fresenius can be minimised by the administration of lidocaine prior to the propofol emulsion and by the use of larger veins of the forearm and

antecubital fossa (see section 4.2 Method of administration). Upon administration of lidocaine the following undesirable effects may occur rarely (≥1/10,000 to <1/1,000): giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.
Rare:
Cases of post-operative fever

Very rare:
There have been reports of isolated cases of severe undesirable effects presenting as a complex of symptoms including: rhabdomyolysis, metabolic acidosis, hyperkalaemia, and cardiac failure, sometimes with fatal outcome. Most of these effects have been observed in patients in intensive care with doses exceeding 4 mg/kg body weight/h. For more detail, see section 4.4 Special warnings and precautions for use.

4.9 Overdose

Overdose is likely to cause cardiovascular and respiratory depression. Respiratory depression is treated with artificial ventilation. Cardiovascular depression may require lowering the patient's head and administering plasma volume substitutes and vasopressive agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics
ATC-Code: NO1AX10

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 - 6 minutes).
With the recommended dosage schedule, a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.

Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

5.2 Pharmacokinetic properties

After intravenous administration about 98 % of propofol is bound to plasma protein.

After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α-phase). The distribution half-life has been calculated as 2 - 4 minutes.

During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

Clearance is higher in children compared with adults.

The central volume of distribution is in the range of 0.2 - 0.79 l/kg body weight, the steady-state volume of distribution in the range of 1.8 - 5.3 l/kg body weight. Propofol is rapidly cleared from the body (total clearance 1.5 to 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive. About 88 % of an administered dose is excreted in the form of metabolites in urine. Only 0.3 % of the administered dose is excreted unchanged in urine.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted. Reproductive toxicity studies have shown effects related to pharmacodynamic properties of propofol only at high doses. Teratogenic effects have not been observed. In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site, paravenous and subcutaneous injection induced histological reactions marked by inflammatory infiltration and focal fibrosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
Triglycerides medium-chain
Purified egg phosphatides
Glycerol
Oleic acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The shelf life of the medicinal product in its original package is 3 years.

The infusion of Propofol 2% (20 mg/1 ml) MCT Fresenius via **one** infusion system must not exceed 12 hours.

After opening the product must be used immediately.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.

6.5 Nature and contents of container

Colourless glass vial (type II) of 50 ml with a bromobutyl rubber closure.

Packs containing 1 glass vial with 50 ml
Packs containing 10 glass vials with 50 ml
Packs containing 15 glass vials with 50 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: to be completed nationally
Date of last renewal: to be completed nationally

10. DATE OF REVISION OF THE TEXT

October 2007

Date of SmPC: Oct 2007