Product Name: Fresofol 2% MCT/LCT	Territory: MY	Colour: ● Black ● Fold lines	1. Draft 08.09.2020, 09.00		Variable Data:
Type of Packaging: Leaflet	Dosage: -				
Material number: M087998/06 MY	2-D-Matrix Code -				
Pharma-Code (Laetus) 3657	EAN Code: -				
Dimension: 170 x 588 mm	Font: Arial Smallest Size: 8.5		Operator: Peter Schaffer		

PACKAGE INSERT - INSTRUCTIONS FOR USE - READ CAREFULLY!

Fresofol 2% MCT/LCT

emulsion for injection or infusion

Composition

1 ml emulsion contains 20 mg propofol.

Each 50 ml vial contains 1000 mg propofol.

Also contains soya-bean oil, triglycerides medium-chain, purified egg phosphatides, glycerol, oleic acid, sodium hydroxide, water for injections

Pharmaceutical form

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

Pharmacodynamics

Pharmacotherapeutic group: Other general anaesthetics
ATC-Code: N01AX10

Propofol (2,6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action. 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 and lasts, depending on the metabolism and elimination, 4 to 6 minutes.

Under the usual maintenance regimen significant accumulation with either repeated injections or infusions of propofol has not been seen. Patients recover consciousness rapidly.

Bradycardia and hypotension reported during induction of anaesthesia may be caused by a cerebral vagotonic effect or inhibition of sympathetic activity. However, haemodynamics generally reverts to normal during maintenance of anaesthesia.

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.

Pharmacokinetics

Propofol is bound to plasma proteins for 98%. Following intravenous administration the pharmacokinetics of propofol can be described by a 3-compartment model.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance: 1.5 to 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.

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).

Therapeutic indications

Fresofol 2% MCT/LCT 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)

Contraindications

Fresofol 2% MCT/LCT must not be used

- in patients with a known hypersensitivity to propofol or to any of the excipients of the emulsion
- in patients who are allergic to soya or peanut
- for sedation in children 16 years of age and younger (see section “Special warnings and precautions for use”)
- must not be used for general anaesthesia in children less than 3 years of age

Use during 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. 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.

Special warnings and precautions for use

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

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

When propofol 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 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. Very rarely the use of propofol may be associated with the development of a period of post-operative 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 agents that may sedate (e.g, benzodiazepines, opiates, alcohol.)

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

Special patient groups

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia

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 clearance is blood flow dependent, therefore, concomitant medication which reduces cardiac output will also reduce propofol clearance.

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of propofol.

Propofol 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.

Propofol 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 is used in conjunction with other agents likely to cause a bradycardia.

Epilepsy
When propofol is administered to an epileptic patient, there may be a risk of convulsion.

There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol. In epileptic patients delayed epileptiform attacks may occur, 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 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.

Use of propofol is not recommended with electroconvulsive therapy.

Patients with disorders of fat metabolism
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

Patients with a high intracranial pressure
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.

Paediatric population

Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care.

Due to the limited data available, the use of target controlled infusion (TCI) in the paediatric population below 2 years of age cannot be recommended.

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 Contraindications).

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 (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 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 Fresofol 2% MCT/LCT contains approximately 0.1 g of fat.

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.

To reduce pain on the injection site during induction of anaesthesia with Fresofol 2% MCT/LCT, lidocaine can be injected prior to the propofol emulsion.
Dilutions with lidocaine solution must not be used in patients with hereditary acute porphyria.

Fresofol 2% MCT/LCT contains soybean oil, which might cause severe allergic reaction in rare cases.

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

Effects on ability to drive and use machines:
After administration of Fresofol 2% MCT/LCT, 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 (please see section Special warnings and precautions for use).

Interactions with other medications

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

Propofol 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 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.

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 Fresofol 2% MCT/LCT 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.

Incompatibilities:

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

Posology and method of administration

Fresofol 2% MCT/LCT 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 Fresofol 2% MCT/LCT should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Fresofol 2% MCT/LCT emulsion should be individualised based on the response of the patient and premedications used.

Supplementary analgesic agents are generally required in addition to Fresofol 2% MCT/LCT.

Posology

- **General anaesthesia in adults:**

Induction of anaesthesia:

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

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Fresofol 2% MCT/LCT 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 Fresofol 2% MCT/LCT 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:**

Induction of anaesthesia:

When used to induce anaesthesia, it is recommended that Fresofol 2% MCT/LCT 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 Fresofol 2% MCT/LCT 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 "Special warnings and precautions for use").

Propofol must not be used for sedation in intensive care of patients of 16 years of age or younger (see section "Contraindications").

Administration of Fresofol 2% MCT/LCT by a Target Controlled Infusion (TCI) system is not advised for sedation in the Intensive Care Unit.

Method of administration

For intravenous use.

Fresofol 2% MCT/LCT is administered undiluted intravenously by continuous infusion. Fresofol 2% MCT/LCT should not be given by repeat bolus injection for maintenance of anaesthesia. When Fresofol 2% MCT/LCT is infused undiluted, 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.

Fresofol 2% MCT/LCT 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 breaking the vial seal. Administration must commence without delay.

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

Fresofol 2% MCT/LCT 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.

Fresofol 2% MCT/LCT must not be administered via a microbiological filter.

Fresofol 2% MCT/LCT and any infusion equipment containing Fresofol 2% MCT/LCT are for **single** administration in an **individual** patient. After use remaining solution of Fresofol 2% MCT/LCT has to be discarded.

As usual for fat emulsions, the infusion of Fresofol 2% MCT/LCT via **one** infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Fresofol 2% MCT/LCT must be discarded or replaced if necessary.

To reduce pain on the injection site, Fresofol 2% MCT/LCT should be administered in a larger vein or lidocaine injection solution may be administered before induction of anaesthesia with Fresofol 2% MCT/LCT.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Fresofol 2% MCT/LCT.

Duration of administration

The duration of administration must not exceed 7 days.

Overdosage

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.

Undesirable effects
Induction and maintenance of anaesthesia or sedation with propofol 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 may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Table of Adverse Drug Reactions

System Organ Class	Frequency	Undesirable Effects
Immune system disorders:	Very rare (<1/10 000)	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and Nutritional disorder:	Frequency not known [9]	Metabolic acidosis [5], hyperkalaemia [5], hyperlipidaemia [5]
Psychiatric disorders:	Frequency not known [9]	Euphoric mood, sexual disinhibition. Drug abuse and drug dependence [8]
Nervous system disorders:	Common (>1/100, <1/10)	Headache during recovery phase
	Rare (>1/10 000, <1/1000)	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery. Vertigo, shivering and sensation of cold during recovery
	Very rare (<1/10 000)	Postoperative unconsciousness
	Frequency not known [9]	Involuntary movements
Cardiac disorders:	Common (>1/100, <1/10)	Bradycardia [1] and tachycardia during induction
	Very rare (<1/10 000)	Pulmonary oedema
	Frequency not known [9]	Cardiac arrhythmia [5], cardiac failure [5], [7]
Vascular disorders:	Common (>1/100, <1/10)	Hypotension [2]
	Uncommon (>1/1000, <1/100)	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders:	Common (>1/100, <1/10)	Transient apnoea, coughing and singultus during induction
	Frequency not known [9]	Respiratory depression (dose dependant)
Gastrointestinal disorders:	Common (>1/100, <1/10)	Nausea and vomiting during recovery phase
	Very rare (<1/10 000)	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	Very rare (<1/10 000)	Discolouration of urine following prolonged administration
	Frequency not known [9]	Renal failure[5]
General disorders and administration site conditions:	Very common (>1/10)	Local pain on induction [4]
	Very rare (<1/10 000)	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	Very rare (<1/10 000)	Postoperative fever
Reproductive system and breast disorders	Frequency not known	Priapism

[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.
[3] Very rare reports of rhabdomyolysis have been received where propofol 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 and/or can also be minimised by the injection of lidocaine immediately before the use of Fresofol 2% MCTLCT.
[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 *Special warnings and precautions for use.*
[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.

Pharmaceutical precautions

Fresofol 2% MCT/LCT should not be used after expiry date.

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.

Administration of the emulsion must commence without delay after breaking the vial seal.

The infusion of undiluted Fresofol 2% MCT/LCT via **one** infusion system must not exceed 12 hours.

For single use. Any unused emulsion must be discarded.

Do not store above 30 °C. Do not freeze.
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.

Presentation

1 and 10 glass vials with 50 ml emulsion for injection or infusion
Not all pack sizes may be marketed.

Manufacturer:

Fresenius Kabi Austria GmbH
Hafnerstraße 36
A-8055 Graz
Austria

Date of Revision:

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FRESENIUS KABI