AUSTRALIAN PRODUCT INFORMATION- FRESOFOL® 1% MCT/LCT (PROPOFOL)

1 NAME OF MEDICINE
Propofol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Fresofol 1% MCT/LCT is a sterile, milky white, isotonic, oil-in-water emulsion for intravenous infusion or injection. 1 mL of Fresofol 1% MCT/LCT contains 10 mg propofol. It also contains the following excipients: soya oil, medium chain triglycerides, glycerol, egg lecithin, sodium hydroxide, oleic acid and water for injections.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM
Injection for emulsion.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Induction of General Anaesthesia in Children and Adults
Fresofol 1% MCT/LCT is a short-acting intravenous anaesthetic agent suitable for induction of general anaesthesia in adults and children aged one month and older.

Maintenance of General Anaesthesia in Children and Adults
Fresofol 1% MCT/LCT is a short acting intravenous anaesthetic agent suitable for maintenance of general anaesthesia in adults and children aged 3 years and older.

Fresofol 1% MCT/LCT may also be used for maintenance of general anaesthesia in children aged from one month to 3 years for procedures not exceeding 60 minutes, unless alternative anaesthetic agents should be avoided.

Fresofol 1% MCT/LCT has no analgesic properties.

Sedation During Intensive Care in Adults
Fresofol 1% MCT/LCT may also be used in adults for sedation of ventilated patients receiving intensive care.

Conscious Sedation for Surgical and Diagnostic Procedures in Adults
Fresofol 1% MCT/LCT may also be used in adults for monitored conscious sedation for surgical and diagnostic procedures.

4.2 Dose and method of administration
Strict aseptic technique must always be maintained during handling. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see also: 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Aseptic Technique).

Adults
Induction of General Anaesthesia
Fresofol 1% MCT/LCT may be used to induce anaesthesia by slow bolus injection or infusion.

In unpremedicated and premedicated patients it is recommended that Fresofol 1% MCT/LCT should be titrated (20 - 40 mg of propofol every 10 seconds) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients less than 55 years are likely to require 1.5 to 2.5 mg of propofol per kg body weight.

In elderly patients, requirements will be generally less (see Elderly Patients). In general, slower rates of infusion at induction results in a lower induction dose requirement and greater haemodynamic stability. In patients of ASA grades III or IV, lower rates of administration should be used (approximately 2 mL, corresponding to 20 mg of propofol every 10 seconds).

Recovery from induction doses usually occurs within 5 to 10 minutes.

Maintenance of General Anaesthesia
Anaesthesia can be maintained by administering Fresofol 1% MCT/LCT either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required. Experience in procedures lasting more than one hour is limited.

Continuous Infusion
The required rate of administration varies considerably between patients but rates in the region of 0.067 to 0.2 mg/kg b.w./min (4 to 12 mg/kg b.w./h) usually maintain satisfactory anaesthesia.

Repeat bolus Injection
If a technique involving repeat bolus injections is used, increments of 25 to 50 mg of propofol (2.5 to 5.0 mL Fresofol 1% MCT/LCT) may be given according to clinical need.

Sedation During Intensive Care
When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Fresofol 1% MCT/LCT should be given by continuous infusion. The infusion rate should be adjusted according to the required depth of sedation. Usually satisfactory sedation is achieved with dosages in the range of 0.3 - 4.0 mg of propofol per kg body weight per hour. Infusion rates greater than 4.0 mg/kg/h are not recommended.

Propofol is contraindicated for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unregistered use. These events were seen more frequently in children with respiratory tract infections (including croup) given doses in excess of those recommended for adults. Lipaemia and an evolving metabolic acidosis may be precursors of fatal outcomes.

Administration of propofol by target controlled infusion (TCI) system is not recommended for sedation during intensive care.

Monitored Conscious Sedation for Surgical and Diagnostic Procedures
Fresofol 1% MCT/LCT is contraindicated for sedation in children as safety and efficacy have not been demonstrated.

To provide sedation for surgical and diagnostic procedures, doses and rates of administration should be individualised and titrated to clinical response. Most patients will require 0.5 - 1 mg of propofol per kg body weight over 1 to 5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating Fresofol 1% MCT/LCT infusion to the desired level of sedation - most patients will require 1.5 - 4.5 mg of propofol per kg bodyweight per hour. In addition to the infusion, bolus administration of 10 - 20 mg of propofol (1 - 2 mL of Fresofol 1% MCT/LCT) may be used if a rapid increase of the depth of sedation is required. In patients in ASA grades III or IV and in the elderly, the rate of administration and dosage may need to be reduced. Patients should not be discharged for at least three hours after the procedure.

Monitored conscious sedation in patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure. Oxygen supplementation should be immediately available and provided where clinically indicated; oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnoea, airway obstruction and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated or ASA grades III or IV patients. Patients should be monitored during sedation and recovered according to the standards of the Australian and New Zealand College of Anaesthetists.

Administration of propofol by target controlled infusion (TCI) system is not recommended for monitored conscious sedation.

Elderly Patients

In elderly patients the dose requirement for induction of anaesthesia with Fresofol 1% MCT/LCT is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Induction infusion rates of 300 mL/hour (50 mg/min) are associated with less hypotension and apnoea in elderly patients. Where Fresofol 1% MCT/LCT is used for maintenance of anaesthesia or sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades III and IV will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly unventilated patient as this may lead to apnoea.

A rapid bolus may also depress cardiac function.

Paediatric Usage

Induction of General Anaesthesia

Fresofol 1% MCT/LCT is suitable for induction of general anaesthesia in children aged one month and older. Fresofol 1% MCT/LCT is contraindicated for use in infants less than 1 month old.

When used to induce anaesthesia in children, it is recommended that Fresofol 1% MCT/LCT be given slowly until clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg of propofol per kg body weight for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades III and IV.

Maintenance of General Anaesthesia
Fresofol 1% MCT/LCT may also be used for maintenance of general anaesthesia in children aged from one month to 3 years. Duration of use in maintenance studies in children under 3 years of age was mostly approximately 20 minutes, with a maximum duration of 75 minutes. A maximum duration of use of approximately 60 minutes should therefore not be exceeded except where there is a specific indication for longer use (e.g. malignant hyperthermia where volatile agents must be avoided). Fresofol 1% MCT/LCT is not recommended for use in infants less than 1 month old. For maintenance of general anaesthesia, a satisfactory level of anaesthesia is usually achieved by continuous infusion with a dosage regimen in the range of 9 - 15 mg of propofol per kg body weight per hour. Younger children less than 3 years may need higher dosages within the range of recommended dosages when compared with older paediatric patients. Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia.

Sedation During Intensive Care
Fresofol 1% MCT/LCT is contraindicated for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unregistered use. These events were seen more frequently in children with respiratory tract infections (including croup) given doses in excess of those recommended for adults. Lipaemia and an evolving metabolic acidosis may be precursors of fatal outcomes.

Children are at particular risk of fat overload. Therefore serum lipids should be monitored in children receiving Fresofol 1% MCT/LCT.

Supplementary analgesic agents are generally required in addition to Fresofol 1% MCT/LCT. Following infusion of Fresofol 1% MCT/LCT, discontinuation of these analgesic agents should be gradual to minimise the risk of withdrawal symptoms.

Monitored Conscious Sedation for Surgical and Diagnostic Procedures
Fresofol 1% MCT/LCT is contraindicated for sedation in children as safety and efficacy have not been demonstrated.

Administration (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Fresofol 1% 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-oxymeter) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times. For sedation during surgical or diagnostic procedures Fresofol 1% MCT/LCT should not be given by the same person that carries out the surgical or diagnostic procedure.

Supplementary analgesic drugs are generally required in addition to Fresofol 1% MCT/LCT.

Infusion of undiluted Fresofol 1% MCT/LCT
When administering Fresofol 1% MCT/LCT by continuous infusion, it is recommended that burettes, drop counters, syringe pumps or volumetric infusion pumps, should always be used to control the infusion rates. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of Fresofol 1% MCT/LCT from one infusion system must not exceed 12 hours. The infusion line and the reservoir of Fresofol 1%

MCT/LCT must be discarded and replaced after 12 hours at the latest. Any portion of Fresofol 1% MCT/LCT remaining after the end of infusion or after replacement of the infusion system must be discarded.

Infusion of diluted Fresofol 1% MCT/LCT
For administering infusion of diluted Fresofol 1% MCT/LCT, burettes, drop counters, syringe pumps, 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 Fresofol 1% MCT/LCT.

The maximum dilution must not exceed 1 part of Fresofol 1% MCT/LCT with 4 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration of propofol 2 mg/mL). The mixture should be prepared aseptically immediately prior to administration. The duration of infusion should not exceed 6 hours.

Fresofol 1% MCT/LCT must not be mixed with other solutions for injection or infusion. However, co-administration of Fresofol 1% MCT/LCT together with 5% w/v glucose solution or 0.9% w/v sodium chloride solution via a Y-connector close to the injection site is possible.

In order to reduce pain on initial injection, Fresofol 1% MCT/LCT may be mixed with preservative-free lidocaine injection 1% (mix 20 parts of Fresofol 1% MCT/LCT with up to 1 part of lidocaine injection 1%).

Before giving the muscle relaxants atracurium or mivacurium subsequent to Fresofol 1% MCT/LCT through the same intravenous line, it is recommended that the line be rinsed prior to administration.

Pre-filled syringes
When the pre-filled Fresofol 1% MCT/LCT is to be injected using a syringe pump, appropriate compatibility should be ensured.
For use with the Fresenius Kabi Agilia® Syringe Pump, select the “Kabifill” syringe option. If your syringe pump does not feature this option, please contact our Customer Service Department at Fresenius Kabi for an update to your pumps.

Instructions for use for pre-filled syringe
Maintain asepsis. The exterior of the syringe and the plunger rod are not sterile.

1. Remove syringe from the blister pack and shake well.
2. Insert the plunger rod by screwing it clock-wise completely into the syringe.
3. Remove cap from syringe. Remove excess air from syringe (a small bubble can remain). Connect syringe to infusion line and load assembled syringe into the Fresenius Kabi Agilia® Syringe Pump.

Fresofol 1% MCT/LCT in pre-filled syringe has not been examined by the TGA for use with Target Controlled Infusion.

Duration of use
Fresofol 1% MCT/LCT can be administered for a maximum period of 7 days.

4.3 Contraindications
Fresofol 1% MCT/LCT is contraindicated:

- in patients with a known hypersensitivity to propofol or to any of the other ingredients contained in Fresofol 1% MCT/LCT, namely soya oil, medium chain triglycerides, glycerol, egg lecithin, sodium hydroxide and oleic acid,
- in patients who are allergic to soya or peanut,
- in children younger than 1 month for induction and maintenance of anaesthesia,
- in patients of 16 years of age or younger for sedation during intensive care and for monitored conscious sedation for surgical and diagnostic procedures.

4.4 Special warnings and precautions for use

In-use precautions

Fresofol 1% MCT/LCT is administered intravenously by injection or continuous infusion either undiluted or diluted with 5% w/v glucose solution or 0.9% w/v sodium chloride solution in glass infusion bottles.

Containers should be shaken before use.

If two layers can be seen after shaking the product, it should not be used.

Before use, the neck of the ampoule or rubber membrane on the vial should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.

Fresofol 1% MCT/LCT contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Fresofol 1% MCT/LCT is to be drawn up aseptically into a sterile syringe or an infusion set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Fresofol 1% MCT/LCT and the infusion equipment throughout the infusion period.

Any drugs or fluids added to a running Fresofol 1% MCT/LCT infusion must be administered close to the cannula site. Fresofol 1% MCT/LCT must not be administered via infusion sets with microbiological filters.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same IV line as Fresofol 1% MCT/LCT without prior flushing.

Monitoring, facilities

As with all anaesthetic procedures, Fresofol 1% MCT/LCT should be given by those trained in anaesthesia (or where appropriate, doctors trained in the care of patients in Intensive Care). Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Fresofol 1% MCT/LCT should not be administered by the person conducting the diagnostic or surgical procedure.

As with other general anaesthetics, the administration of propofol without airway care may result in fatal respiratory complications. When Fresofol 1% MCT/LCT is administered as a sedative for surgical or diagnostic procedures, patients should be continuously monitored by persons not involved in the conduct of the surgical / diagnostic procedures. Oxygen supplementation should be immediately available and provided when clinically indicated; oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnoea, airway obstruction and/or oxygen desaturation.

These cardio-respiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated

and ASA (American Society of Anesthesiologists) grades III or IV patients and with co-administration of other sedatives and opioid agents. Monitoring during the procedure and during the recovery period should be in accordance with the needs of the patient.

Fresofol 1% MCT/LCT should be administered with caution when Fresofol 1% MCT/LCT is used for sedation during operative procedures, since involuntary patient movements may occur. During procedures requiring immobility, such as ophthalmic surgery, these movements may be hazardous to the operative site.

Abuse Potential
The abuse of propofol, predominantly by health care professionals, has been reported.

Premedication
During induction of anaesthesia, hypotension and apnoea, similar to effects with other intravenous anaesthetic agents, commonly occur and may be influenced by the rate of administration, the use of premedicants and other agents, including benzodiazepines.

Fresofol 1% MCT/LCT 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 Fresofol 1% MCT/LCT is used in conjunction with other agents likely to cause a bradycardia (see also 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Ventilatory depression can occur following administration of Fresofol 1% MCT/LCT. An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of Fresofol 1% MCT/LCT may be associated with the development of unconsciousness after the period when recovery from anaesthesia should have occurred. This may be accompanied by an increase in muscle tone and may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

Special care should be taken in patients with a high intracranial pressure and a low arterial pressure as Fresofol 1% MCT/LCT reduces cerebral blood flow, intracranial pressure and cerebral metabolism. This reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Concomitant Disease States
As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic, debilitated or epileptic patients. In patients with severe cardiac impairment it is recommended that Fresofol 1% MCT/LCT is given with great caution and under intensive monitoring.

If possible, hypovolaemia, cardiac insufficiency, circulatory depression or impaired respiratory function should be compensated before the administration of Fresofol 1% MCT/LCT.

Elevation of Serum Triglycerides

Appropriate care should be paid to disorders of fat metabolism or to diseases requiring particularly restrictive use of lipid emulsions. Because Fresofol 1% MCT/LCT is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when Fresofol 1% MCT/LCT is administered for extended periods of time. Fresofol 1% MCT/LCT contains medium-chain triglycerides (MCT) 50 mg/mL and long-chain triglycerides (LCT) 50 mg/mL. Metabolism of medium chain triglycerides (MCTs) differs from that of long-chain triglycerides (LCT). Unlike longer-chain fatty acids, MCT require little carnitine for mitochondrial entry, and their more rapid breakdown may impart an increased production of ketones. It is recommended that the impact of total fat administration and infusion rate be considered in patients receiving Fresofol 1% MCT/LCT in conjunction with other fat-containing products such as parenteral nutrition agents, especially in patients demonstrating disturbances in normal fat metabolism. Patients at risk of hyperlipidaemia should be monitored for increases in serum triglycerides or serum turbidity. The dosage and infusion rate should be within the ranges recommended. Too rapid infusion of Fresofol 1% MCT/LCT could lead to hyperketonaemia and/or metabolic acidosis. Administration of Fresofol 1% MCT/LCT should be adjusted if lipids are being cleared inadequately from the body. A reduction in the quantity of concurrently administered lipids is indicated to compensate for the amount of lipid infused as part of the Fresofol 1% MCT/LCT formulation; 1.0 mL of Fresofol 1% MCT/LCT contains 0.1 g of fat (see also section 4.2 DOSE AND METHOD OF ADMINISTRATION, Sedation During Intensive Care).

Lipids should be monitored in ICU treatment after 3 days.

Fresofol 1% MCT/LCT provides approximately 1.1 kcal/mL.

Epilepsy

Propofol has been found to have no effect on electroshock seizure threshold in animals. When propofol injection is administered to an epileptic patient, there may be a risk of seizure during the recovery phase. Before anaesthesia of an epileptic patient, it should be checked that the patient has received the antiepileptic treatment. Perioperative myoclonia less frequently including convulsions and opisthotonus, has occurred in temporal relationship in cases in which propofol has been administered.

Use is not recommended with electroconvulsive therapy.

As with thiopentone, in vitro studies have shown that propofol is much less potent than etomidate in the inhibition of synthesis of adrenocorticohormones. At concentrations of propofol likely to be encountered in anaesthetic practice, no clinically significant effect on adrenocorticohormones has been noted in studies to date.

Anaphylactoid Reactions

Propofol has been reported to occasionally cause clinical anaphylactic / anaphylactoid type of reactions with angioedema, bronchospasm, erythema and hypotension. These reactions have been reported to respond to adrenaline.

Use for Sedation During Intensive Care

When propofol is used for sedation during intensive care the following life-threatening adverse events known as Propofol Infusion Syndrome (PRIS), can occur together or in combinations: cardiac failure, arrhythmias, metabolic acidosis, rhabdomyolysis, ECG changes* and/or rapidly progressive cardiac failure (in some cases with a fatal outcome), hyperkalaemia, hepatomegaly, hyperlipidemia and renal failure.

There have been very rare reports of occurrence of PRIS in adults (in some cases with a fatal outcome) treated for more than 48 hours with propofol infusions in excess of 5 mg/kg/hour have been reported. These reports have mainly (but not exclusively) been in patients with serious head injuries treated with high doses of propofol, inotropes and vasoconstrictors. The following appear to be 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. If these adverse events occur unexpectedly in the presence of high infusion rates of propofol, or hypertriglyceridaemia / lipidaemia is detected, consideration should be given to decreasing the propofol dosage or switching to an alternative sedative. In the event of propofol dosage modification, patients with raised intracranial pressure should continue to be monitored and treated appropriately as should patients with metabolic, respiratory and/or haemodynamic disturbances. The risk of these life-threatening events occurring may be increased in the presence of persistent low cardiac output. The maximum dose of propofol for adult sedation during intensive care should not exceed 4.0 mg/kg/hour (see 4.2 DOSE AND METHOD OF ADMINISTRATION).

The safety and efficacy of propofol for (background) sedation in children 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, hyperlipidaemia, 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.

The use of propofol for sedation in children 16 years of age and younger during intensive care and for sedation for surgical and diagnostic procedures in children younger than 1 month is contraindicated (see 4.3 CONTRAINDICATIONS).

<u>Aseptic Technique (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION)</u>

Strict aseptic technique must always be maintained during handling. Fresofol 1% MCT/LCT contains no antimicrobial preservatives and supports growth of microorganisms. Fresofol 1% MCT/LCT is to be drawn up aseptically into a sterile syringe or an infusion set immediately after opening the ampoule or breaking the vial seal. Before use, the neck of the ampoule or rubber membrane on the vial should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.

Administration must commence without delay. Asepsis must be maintained for both Fresofol 1% MCT/LCT and the infusion equipment throughout the infusion period.

Any drugs or fluids added to a running Fresofol 1% MCT/LCT infusion must be administered close to the cannula site. Fresofol 1% MCT/LCT must not be administered via infusion sets with microbiological filters.

The contents of one ampoule or vial of Fresofol 1% MCT/LCT and any syringe containing Fresofol 1% MCT/LCT are for single use in one patient. Any portion of the contents remaining after use must be discarded. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of Fresofol 1% MCT/LCT from one infusion system must not exceed 12 hours. The infusion line and the reservoir of Fresofol 1% MCT/LCT must be discarded and replaced after 12 hours at the latest. Any portion of Fresofol 1% MCT/LCT remaining after the end of infusion or after replacement of the infusion system must be discarded.

Use in the Elderly

Refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION- Elderly Patients.

Paediatric Use

Use in Children

There are no clinical trials to support the use of propofol for the sedation of children with croup or epiglottitis receiving intensive care.

Use in Neonates

(see also Section 4.2 DOSE AND METHOG OF ADMINISTRATON and Section 4.3 CONTRAINDICATIONS)

Fresofol 1% MCT/LCT is not recommended for induction and maintenance of anaesthesia in neonates.

There are no data to support the use of propofol for the sedation of premature neonates receiving intensive care.

Paediatric Neurotoxicity

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

Effects on Laboratory Tests

No data available.

Others

Due to the higher doses usually applied in gross overweight patients, care should be taken regarding the increased risk of adverse haemodynamic effects.

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

4.5 Interactions with other medicines and other forms of interactions

As with other intravenous sedative agents, when propofol is given with central nervous system depressants, such as potent analgesics, alcohol, or general anaesthetics, the sedative effect may be intensified and the possibility of severe respiratory or cardiovascular depression should be considered. Concomitant use of benzodiazepines, parasympatholytic agents or inhalation anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

The induction dose requirements of Fresofol 1% MCT/LCT may be reduced in patients with intramuscular or intravenous premedication (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Premedication), particularly with narcotics (e.g. morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.) These agents may increase the anaesthetic or sedative effects of Fresofol 1% MCT/LCT and may also result in more pronounced decreases in systolic, diastolic and mean arterial pressures and cardiac output. Decreased oxygen saturation has been reported when propofol is administered with fentanyl, for this reason oxygen supplementation should be used.

After additional premedication with opioids there may be a higher incidence and longer duration of apnoea. After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

During maintenance of anaesthesia or sedation, the rate of Fresofol 1% MCT/LCT administration should be adjusted according to the desired level of anaesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g. nitrous oxide or opioids). The concurrent administration of potent inhalational agents (e.g. isoflurane, enflurane, and halothane) during maintenance with Fresofol 1% MCT/LCT has not been extensively evaluated.

These inhalational agents can also be expected to increase the anaesthetic or sedative and cardiorespiratory effects of Fresofol 1% MCT/LCT.

Propofol does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g. suxamethonium and nondepolarizing muscle relaxants).

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

No significant adverse interactions with commonly used premedications or drugs used during anaesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anaesthetic agents) have been observed.

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

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

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

Studies in female rats at intravenous doses up to 15 mg/kg/day for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Use in pregnancy (Category C)
All general anaesthetics cross the placenta and carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice this does not appear to be a problem. However, in the compromised foetus careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

Fresofol 1% MCT/LCT should not be used in pregnancy. Teratology studies in rats and rabbits show some evidence of delayed ossification or abnormal cranial ossification with an increase in the incidence of subcutaneous haematomas. Reproductive studies in rats suggest that administration of propofol to the dam adversely affects perinatal survival of the offspring.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

Obstetrics

Propofol crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia.

Use in lactation
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

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia. Patients must be accompanied when going home after discharge and must be instructed to avoid drinking alcohol.

4.8 Adverse effects (Undesirable effects)

The most commonly observed adverse 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.

During induction in clinical trials with a product containing propofol which is interchangeable with Fresofol 1% MCT/LCT, hypotension and transient apnoea occurred in up to 75% of patients. Excitatory phenomena such as involuntary movements, twitches, tremors, hypertonus and hiccup occurred in 14% of patients. Bradycardia responsive to atropine has been reported.

During the recovery phase, vomiting, headache and shivering occurred in about 2% of the patients with nausea occurring more frequently.
Specifically, the following side effects have been observed:

Table 1 - 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, drug abuse [8]
Nervous system disorders:	Common (>1/100, <1/10)	Headache during recovery phase. During induction of anaesthesia spontaneous movements and myocloni are likely to be observed.
	Uncommon (>1/1000, <1/100)	Dystonia and other involuntary movement disorders.
	Rare (>1/10 000, <1/1000)	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery. Convulsions and seizures of the epileptic type.
	Very rare (<1/10 000)	Delayed epileptiform attacks, the delay period ranging from a few hours to several days. Convulsions have been observed in epileptic patients after administration of propofol (isolated cases). Cases of postoperative unconsciousness.
	Frequency not known [9]	Involuntary movements
Cardiac disorders:	Common (>1/100, <1/10)	Bradycardia [1] Mild or moderate hypotension

	Uncommon (>1/1000, <1/100)	Marked hypotension
	Rare (>1/10 000, <1/1000)	Arrythmias during the recovery period. Bradycardia during general anaesthesia in some cases with progressive severity (up to asystole). The intravenous administration of an anticholinergic drug prior to induction or during maintenance of anaesthesia should be considered.
	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
	Rare (>1/10 000, <1/1000)	Thrombosis, phlebitis
Respiratory, thoracic and mediastinal disorders:	Common (>1/100, <1/10)	Transient apnoea, cough and hyperventilation during induction of anaesthesia.
	Uncommon (>1/1000, <1/100)	Coughing during maintenance of anaesthesia.
	Rare (>1/10 000, <1/1000)	Coughing during the recovery period.
	Very rare (<1/10 000)	Pulmonary oedema (isolated cases)
Gastrointestinal disorders:	Common (>1/100, <1/10)	Nausea and vomiting during recovery phase.
	Rare (>1/10 000, <1/1000)	Nausea or vomiting during the recovery period.

	Very rare (<1/10 000)	Pancreatitis occurred after administration of propofol. A causal relationship, however, could not be established.
Hepatobiliary disorders	Frequency not known [9]	Hepatomegaly [5]
Musculoskeletal and connective tissue disorders:	Frequency not known [9]	Rhabdomyolysis [3], [5]
Renal and urinary disorders	Rare (>1/10 000, <1/1000)	Discolouration of urine on prolonged use.
	Very rare (<1/10 000)	Discolouration of urine following prolonged administration.
	Frequency not known [9]	Renal failure [5]
Reproductive system and breast	Very rare (<1/10 000)	Sexual disinhibition, Priapism
General disorders and administration site conditions:	Very common (>1/10)	Pain during initial injection (burning, tingling/stinging)[4]
	Common (>1/100, <1/10)	Hiccup during induction of anaesthesia.
	Rare (>1/10 000, <1/1000)	Cases of post-operative fever, headache, vertigo, shivering and sensations of cold during the recovering period, euphoria. Anaphylactoid/ anaphylactic reactions, in some cases with angiooedema, bronchospasm, erythema and hypotension (These reactions have been reported to respond to adrenaline).
	Very rare (<1/10 000)	Severe tissue reactions after accidental extravascular administration (isolated cases).
Investigations	Frequency not known [9]	Brugada type ECG [5], [6]
Injury, poisoning and procedural complications:	Very rare (<1/10 000)	Postoperative fever

Skin	Common (>1/100, <1/10)	Hot flushes during induction of anaesthesia.

(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. With Propofol local pain can also be minimised by the co-administration of lidocaine. (see also: ADMINISTRATION). After co-administration of lidocaine the following undesirable effects may occur: giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.
(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) Drug abuse, predominantly by health care professionals.
(9) Not known as it cannot be estimated from the available clinical trial data.

Propofol infusion syndrome
Symptoms of PRIS include: Metabolic acidosis, notably lactic acidosis, hyperlipidaemia, hyperkalaemia, rhabdomyolysis typically indicated by a marked increase of the blood creatine phosphokinase, renal impairment or failure and cardiac failure not responding to inotropic medication. Cases of fatal outcome have been reported. Of note, the propofol infusion syndrome may present with varying combinations of the symptoms listed here. (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use for Sedation During Intensive Care).

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.

Epileptiform movements, including convulsions and opisthotonus, have occurred. As with other anaesthetic agents, depression of cardiac output may occur. As with other anaesthetics, sexual disinhibition may occur during recovery. Depression, crying, confusion, restlessness, broncho or laryngospasm were also observed.

Following abrupt discontinuation of Fresofol 1% MCT/LCT in children receiving intensive care, withdrawal symptoms and flushing have been noted. Cardiorespiratory depression may occur in neonates if paediatric dosage regimen is used for induction of anaesthesia.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. The majority of pharmacodynamic properties exhibited by propofol are proportional to the dose or concentration in the blood. These dose or dose rate dependent properties include the desired therapeutic effects of mild sedation through to anaesthesia, but also include the increasing incidence of cardiac and respiratory depression seen with increasing dose.

The cardiovascular effects of propofol range from a minimal reduction in blood pressure through to arterial hypotension, and a decrease in heart rate. 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, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

Preliminary findings in patients with normal intraocular pressure indicate that propofol anaesthesia produces a decrease in intra-ocular pressure, which may be associated with a concomitant decrease in systemic vascular resistance.

In combination with hypocarbia, propofol increases cerebro-vascular resistance, decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure; but does not affect cerebro-vascular reactivity to changes in arterial carbon dioxide tension.

Limited experience in susceptible patients does not indicate any propensity of propofol to induce malignant hyperthermia.

Propofol does not suppress the adrenal response to adrenocorticotropic hormone (ACTH).

Clinical trials

No data available.

5.2 Pharmacokinetic properties

The pharmacokinetics of propofol follow a three compartment open model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues.

Absorption
Following an intravenous (IV) bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anaesthesia.

Distribution
Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. The initial (distribution) half-life is between 2 and 4 minutes, followed by a rapid elimination phase with a half-life of 30 - 60 minutes and followed by a slower final phase, representative of redistribution of propofol from poorly perfused tissue. Accumulation may occur if higher than necessary infusion rates are used.

Metabolism
Propofol is primarily metabolised by the liver to predominately glucuronide conjugates and their corresponding quinols, which are inactive and are excreted renally. The pharmacokinetics of propofol are linear over the recommended range of infusion rates of Fresofol 1% MCT/LCT. Moderate hepatic or renal impairment do not alter these pharmacokinetics. Patients with severe hepatic or renal impairment have not been adequately studied.

Excretion
Adult propofol clearance ranges from 1.5 - 2 litres/minute (21 - 29 mL/kg/min).

The distribution and clearance in children down to the age of three years are similar to those of adults. In infants from one month to three years, the clearance of propofol has shown to be higher than children three years and older. Infants may require an increased dose but is not significantly greater than the dose for children between 3 and 8 years of age.

In older patients for a given dose, a higher peak plasma concentration is observed. The VD (Volume of Distribution) and clearance are also decreased; this may explain the decreasing dose requirement with increasing age and the sensitivity of older patients to the other dose related effects of propofol.

Discontinuation of propofol after the maintenance of anaesthesia for approximately one hour, or ICU (Intensive Care Unit) sedation for one day, results in a prompt decrease in blood propofol concentrations and rapid awakening, usually within 5 minutes. Longer infusions (10 days of ICU sedation) result in accumulation of significant tissue stores of propofol, such that the reduction in circulating propofol is slowed and the time to awakening may be increased by up to 15 minutes.

5.3 Preclinical safety data

Genotoxicity

Propofol was not genotoxic in a series of assays for gene mutation (Salmonella typhimurium and Saccharomyces cerevisiae), chromosomal damage (dominant lethal, micronucleus and cytogenetics assays) and other genotoxic effects (Saccharomyces cerevisiae gene conversion).

Carcinogenicity

Animal carcinogenicity studies have not been performed with propofol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya oil, medium chain triglycerides, glycerol, egg lecithin, sodium hydroxide, oleic acid and water for injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25 °C.
Do not freeze.

6.5 Nature and contents of container

This product is supplied in:

- 20 mL (200 mg/20 mL propofol) in a colourless glass ampoule
- 20 mL (200 mg/20 mL propofol) in a colourless glass vial with a halobutyl rubber closure sealed with an aluminium-plastic flip-off cap
- 50 mL (500 mg/50 mL propofol) in a colourless glass vial with a halobutyl rubber closure sealed with an aluminium-plastic flip-off cap
- 50 mL (500 mg/50 mL propofol) in a colourless cyclo-olefine-copolymer pre-filled syringe with bromobutyl rubber tip cap and plunger provided with a polypropylene plunger rod
- 100 mL (1000 mg/100 mL propofol) in a colourless glass vial with a halobutyl rubber closure sealed with an aluminium-plastic flip-off cap

Packs containing 5 x 20 mL glass ampoules
Packs containing 10 x 20 mL glass ampoules
Packs containing 5 x 20 mL glass vials
Packs containing 10 x 50 mL or 100 mL glass vials
Pack containing 1 x 50 mL plastic pre-filled syringe

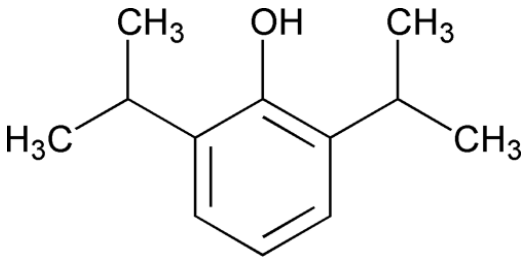
Not all pack sizes may be marketed in Australia.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Chemical name: 2,6-diisopropylphenol

CAS number

2078-54-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: S4 - Prescription Only Medicine

8 SPONSOR

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Mount Kuring-gai, NSW 2080
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Telephone: (02) 9391 5555

9 DATE OF FIRST APPROVAL

23 Nov 2012

10 DATE OF REVISION

2 Feb 2023

Summary table of changes

Section Changed	Summary of new information
Section 4.4	Minor editorial changes Order of text rearranged within the same section
Section 4.6	"Obstetrics" moved from Section 4.4 over to 4.6.
Section 4.8	Adverse Drug Reactions presented in a Table Added the adverse event "priapism" Minor editorial changes
Section 7	NZ details removed
Section 8	NZ details removed