

AUSTRALIAN PRODUCT INFORMATION

FRESOFOL® 1 % (PROPOFOL)

1 NAME OF MEDICINE

Propofol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of Fresofol 1% injection contains propofol 10 mg. It also contains; soya oil and egg lecithin.

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Propofol is a clear colourless to straw yellow liquid with a typical odour. Fresofol 1% injection is a white, isotonic (oil-in water) emulsion and is designed for intravenous injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fresofol 1% is a short-acting intravenous anaesthetic agent suitable for the induction of general anaesthesia in adults and children aged three years and older. Fresofol 1% has no analgesic properties.

Although safety and efficacy of Fresofol 1% in paediatric day surgery have not been demonstrated, it may be a useful agent in this setting and its use should not be precluded.

Fresofol 1% may also be used in adults for the sedation of ventilated patients receiving intensive care.

Fresofol 1% may also be used in adults for monitored conscious sedation for surgical and diagnostic procedures.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage and Administration (see also Aseptic Technique)

Strict aseptic technique must always be maintained during handling. Fresofol 1% injection is a single patient use only parenteral product which does not contain any antimicrobial preservative. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE- Aseptic Technique and 6.3 SHELF LIFE). There have been reports in which failure to use aseptic technique when handling Fresofol 1% injection was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

ADULTS

- a) Induction of general anaesthesia

Fresofol 1% may be used to induce anaesthesia by slow bolus injection or infusion. In unpremedicated and in premedicated patients, it is recommended that Fresofol 1% should be titrated (approximately 4 mL (40 mg) every 10 seconds in an average healthy adult) 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 2.0 to 2.5 mg Propofol/kg body weight.

Over this age, the requirement will be generally less (see Use in the elderly). 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 and IV, lower rates of administration of Fresofol 1% should be used (approximately 2 mL (20 mg) every 10 seconds).

b) Maintenance of general anaesthesia

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

Continuous infusion

For maintenance of anaesthesia using continuous infusion doses, the required rate of administration varies considerably between patients, but rates in the region of 0.067 to 0.2 mg/kg/min (4 to 12 mg Propofol/kg body weight per hour) usually maintain satisfactory anaesthesia. A reduced maintenance dose of approximately 4 mg Propofol/kg/ bodyweight per hour may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

Repeat Bolus Injections

For maintenance of anaesthesia using repeat bolus injections dose increments of 25 to 50 mg Propofol (2.5-5 mL Fresofol 1%) may be given according to clinical need.

Time to recovery

Recovery from induction doses usually occurs within 5 to 10 minutes. Recovery from induction doses (2 to 2.5 mg of propofol per kg) and maintenance (with 0.1 to 0.2 mg of propofol per kg per minute) for up to 2 hours occurs in most patients within eight minutes. If an opioid has been used, recovery may take up to 19 minutes.

c) Sedation in adults during intensive care

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Fresofol 1% be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 1.0 to 3.0 mg/kg/h should achieve satisfactory sedation. Infusion rates greater than 4.0 mg/kg/h are not recommended.

d) Monitored Conscious Sedation for Surgical and Diagnostic Procedures

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

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating Fresofol 1% infusion to the desired level of sedation – most patients will require 1.5 to 3.0 mg/kg/h. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required. In patients in ASA grades III or IV (according to the classification of the American Society of Anaesthesiologists) 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.

Use in the elderly

In elderly patients the dose requirement for induction of anaesthesia with Fresofol 1% 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 hypertension and apnoea in elderly patients. Where Fresofol 1% 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.

USE IN CHILDREN (over 3 years of age)

Children are at particular risk of fat overload. Therefore serum lipids should be monitored in children receiving propofol.

Supplementary analgesic agents are generally required in addition to propofol. Following infusion of propofol, discontinuation of these analgesic agents should be gradual to minimise the risk of withdrawal symptoms.

a) Induction of general anaesthesia

Due to lack of experience Fresofol 1% must not be used in children under 3 years of age.

When used to induce anaesthesia, it is recommended that Fresofol 1% should be titrated slowly until the clinical signs show the onset of anaesthesia.

The dose should be adjusted for age and/or 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 requirements may be more. Lower dosage is recommended in children of ASA grades III and IV.

b) Maintenance of anaesthesia

Fresofol 1% is not recommended for use in children less than three years of age. Anaesthesia can be maintained by administering Fresofol 1% by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

c) Sedation during intensive care

Fresofol 1% 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.

d) Monitored conscious sedation for surgical and diagnostic procedures

Fresofol 1% is contraindicated for sedation in children as safety and efficacy have not been demonstrated.

Administration (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Fresofol 1% is a lipid containing emulsion without an antimicrobial preservative and may support rapid growth of micro-organisms. Ampoules and vials of Fresofol 1% are to be shaken before use. The emulsion must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay.

Asepsis must be maintained for both Fresofol 1% and infusion equipment throughout the infusion period. Fresofol 1% must not be administered via a microbiological filter.

Fresofol 1% and any infusion equipment containing Fresofol 1% are for single administration in an individual patient. Any portion of the contents remaining after use should be discarded.

Changes to the haemodynamic parameters such as systolic arterial pressure, diastolic arterial pressure, cardiac output and systemic vascular resistance appear to be independent to changes to rate of infusion of propofol.

Infusion of undiluted Fresofol 1%

When Fresofol 1% is infused undiluted to maintain anaesthesia, it is recommended that equipment such as drop counter, syringe pumps or volumetric infusion pumps should always be used in control infusion rates.

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

Infusion of diluted Fresofol 1%

The dilution may be used with a variety of infusion control techniques, but a giving set used alone will not avoid the risk of accidental uncontrolled infusion of large volumes of diluted Fresofol 1%. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum dilution in the burette.

Dilutions, which must not exceed 1 part of Fresofol 1% and 4 parts of Glucose 5% intravenous infusion solution (at least 2 mg Fresofol 1% per mL) should be prepared aseptically immediately before administration. It is recommended that in order to prepare diluted Fresofol 1%, the volume of 5% Glucose (Intravenous Infusion BP) removed from the infusion bag during the dilution process be totally replaced in volume by Fresofol 1%. Unused portions of the injection as well as reservoirs, IV lines or solutions containing propofol injection, must be discarded at the end of the procedure or within 6 hours, whichever occurs sooner.

Fresofol 1% may be administered via a Y-piece close to the injection site, into infusions of Glucose 5% (Intravenous Infusion B.P.), Sodium Chloride 0.9% (Intravenous Infusion B.P.), or Glucose 4% with Sodium Chloride 0.18% (Intravenous Infusion B.P.).

Fresofol 1% should not be mixed prior to administration with other therapeutic agents or infusion fluids other than 5% glucose (Intravenous Infusion B.P.). Muscle relaxants like atracurium and mivacurium should not be given through the same intravenous line as Fresofol 1% without prior flushing.

4.3 CONTRAINDICATIONS

Fresofol 1% is contraindicated in patients with hypersensitivity to egg-, soya- or peanut protein or to any of the other ingredients contained in Fresofol 1% (see section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and 6.1 LIST OF EXCIPIENTS).

Fresofol 1% is contraindicated during pregnancy, breast feeding and obstetrics (except abortion).

Fresofol 1% is contraindicated for general anesthesia in children less than three years of age.

Fresofol 1% is contraindicated in children 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

Monitoring facilities

Fresofol 1% should be given by a physician trained in anaesthesia (or where

appropriate, physicians trained in the care of patients in Intensive Care). Fresofol 1% should not be administered by the person conducting the diagnostic or surgical procedure. When Fresofol 1% is administered as a sedative for surgical or diagnostic procedures, patients should be continuously monitored by persons not involved in the conduct of the diagnostic or surgical procedure. 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 cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated and ASA 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. Facilities for maintenance of a patent airway, artificial oxygen enrichment and other resuscitation facilities should be readily available at all times.

When Fresofol 1% 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.

Premedication

As with other intravenous anaesthetic agents, hypotension and apnoea during induction of anaesthesia commonly occur and may be influenced by the rate of administration, use of other premedications and other agents including benzodiazepines.

Fresofol 1% lacks vagolytic activity and has been associated with bradycardia (occasionally profound) (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) 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% is used in conjunction with other agents likely to cause bradycardia (See section 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% during the period of anaesthetic maintenance.

Ventilatory depression can occur following administration of Fresofol 1%.

Fresofol 1% reduces cerebral blood flow, intracranial pressure and cerebral metabolism. This reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

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% 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.

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 or debilitated patients.

Elevation of Serum Triglycerides

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

Because Fresofol 1% injection is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when Fresofol 1% injection is administered for extended periods of time. Patients at risk of hyperlipidaemia should be monitored for increases in serum triglycerides or serum turbidity. Administration of Fresofol 1% injection 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% injection formulation; 1.0 mL of Fresofol 1% injection contains approximately 0.1 g of lipid (see also Sedation During Intensive Care).

The calorific value of Fresofol 1% is similar to that of "Intralipid" 10% ie 1.0 mL of Fresofol 1% provides 1.1 kcals.

Epilepsy

Propofol has been found to have no effect on electroshock seizure threshold in animals. When Fresofol 1% injection is administered to an epileptic patient, there may be a risk of seizure during the recovery phase. Perioperative myoclonia less frequently including convulsions and opisthotonus, has occurred in temporal relationship in cases in which Fresofol 1% injection has been administered.

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 Fresofol 1% likely to be encountered in anaesthetic practice, no clinically significant effect on adrenocorticohormones has been noted in studies to date.

Anaphylactoid Reactions

Fresofol 1% 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

Life threatening adverse events, occurring together or in combinations, of cardiac failure, arrhythmias, metabolic acidosis, rhabdomyolysis and renal failure associated with propofol when used in sedation during intensive care.

There have been very rare reports of metabolic acidosis, rhabdomyolysis,

hyperkalaemia, and/or rapidly progressive cardiac failure (in some cases with a fatal outcome) in adults treated for more than 48 hours with propofol infusions in excess of 5 mg/kg/hour. These reports have mainly (but not exclusively) been in patients with serious head injuries treated with high doses of propofol, inotropes and vasoconstrictors. These reports also indicated that a failure of oxygen delivery to the tissues was likely to have occurred. 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 section 4.2 DOSE AND METHOD OF ADMINISTRATION]. The use of propofol for sedation in children 16 years of age and younger during intensive care and for monitored conscious sedation for surgical and diagnostic procedures is contraindicated [see section 4.3 CONTRAINDICATIONS].

Use in the Elderly

No data available.

Obstetrics

Fresofol 1% crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia.

Paediatric Use

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

Use in neonates

Propofol is not recommended for induction and maintenance of anaesthesia in neonates.

Effects on laboratory Testing

No data available.

Induction Phase

At induction, the dose requirements of Fresofol 1% injection may be reduced in patients with intramuscular or intravenous premedications (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE- Premedication), particularly with narcotics (e.g. morphine, meperidine and fentanyl) and combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate, droperidol). These agents may increase the anaesthetic or sedative effects of Fresofol 1% injection 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 Fresofol 1% is administered with fentanyl; therefore oxygen supplementation should be used.

Maintenance Phase

During maintenance of anaesthesia or sedation, the rate of Fresofol 1% injection 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% injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anaesthetic or sedative and cardiorespiratory effects of Fresofol 1% injection.

Aseptic Technique (See also Pharmaceutical Precautions))

Strict aseptic technique must always be maintained during handling. Fresofol 1% injection is a single patient use only parenteral product which does not contain any antimicrobial preservative. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions. There have been reports in which failure to use aseptic technique when handling Fresofol 1% injection was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

When Fresofol 1% is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Fresofol 1% and the infusion equipment throughout the infusion period. Any drugs or fluids added to the Fresofol 1% line must be administered close to the cannula site. Fresofol 1% must not be administered via a microbiological filter.

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

Pharmaceutical Precautions (see also Aseptic Technique)

In-use precautions:

Each ampoule or vial should be shaken before use. Do not use if the emulsion is separated or discoloured.

Any portion of the contents remaining after use should be discarded.

The emulsion should not be mixed prior to administration with other therapeutic agents or infusion fluids other than 5% Glucose (Intravenous Infusion B.P.).

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

Special Warnings and Precautions for Use

Use of Fresofol 1% is not recommended with electroconvulsive therapy.

The safety and efficacy of Fresofol 1% 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, 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 ICU. 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 treated for more than 58 hours with dosages in excess of 5 mg/kg/hr. These exceed the maximum dosage of 4 mg/kg/hr currently advised for sedation in the ICU. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

Prescribers are reminded if possible not to exceed the dosage of 4 mg/kg/hr which is usually sufficient for sedation of mechanically ventilated patients in the ICU situation (treatment durations in excess of 1 day). Prescribers should be alert to these possible undesirable effects and decrease the dosage or switch to an alternative sedative at the first sign of occurrence of symptoms.

Fresofol 1% contains soya oil and egg lecithin which may rarely cause severe allergic reactions. Cross allergic reactions have been observed between soya-bean and peanut.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fresofol 1% has been used with commonly used premedications or drugs used during anaesthesia or sedation (including a range of inhalational anaesthetics, analgesics, muscle relaxants or local anaesthetics). No significant adverse interactions have been observed.

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.

When Fresofol 1% is given with CNS depressants (e.g. potent analgesics), the sedative effect may be intensified and the possibility of severe respiratory or cardiovascular depression should be considered.

Fresofol 1% injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg succinylcholine and nondepolarizing muscle relaxants).

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 fetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

Fresofol 1% 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 rat studies suggest that the 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.

Use in lactation

Propofol is reportedly distributed into breast milk. Safety to the child has not been established, therefore Fresofol 1% is contraindicated in mothers who are breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

After administration of Fresofol 1%, 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

During induction of propofol in clinical trials, 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.

Very common (>1/10)

Body as a whole: pain during injection (burning, tingling/stinging)

Common (>1/100, <1/10)

Body as a whole: elation/euphoria, headache, shivering.

Cardiovascular: hypotension, hypertension, bradycardia.

Gastrointestinal: nausea, vomiting.

Respiratory: transient apnoea, cough.

Skin: flush/rash

Uncommon (>1/1000, <1/100)

Cardiovascular: arrhythmias - tachycardia, extrasystole.

Rare (<1/1000)

Body as a whole: fever

Blood: thrombosis, phlebitis

CNS: convulsions and seizures of the epileptic type.

Urogenital: discolouration of the urine on prolonged use.

Other: anaphylactoid reactions, in some cases with angio-oedema, bronchospasm, erythema and hypotension. (These reactions have been reported to respond to adrenaline.)

Very Rare (<1/10000)

Musculoskeletal and connective tissue: rhabdomyolysis (when propofol has been administered at doses greater than 4 mg/kg/hr for ICU sedation).

Gastrointestinal: pancreatitis, abdominal cramps

CNS: pulmonary oedema, post-operative unconsciousness

Other: cough, hiccup

Very rare reports of cardiac failure, metabolic acidosis, renal failure and hyperkalaemia have been reported.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Fresofol 1% during the period of anaesthetic maintenance or sedation.

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% in children receiving intensive care, withdrawal symptoms and flushing have been noted. Cardio-respiratory depression may occur in neonates if paediatric dosage regimen is used for induction of anaesthesia.

Following paravenous application severe tissue responses may occur very rarely.

Intra-arterial injection in animals did not induce local tissue effects.

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 cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patient's head, and in severe cases, the use of plasma expanders and pressor agents.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Propofol is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. 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 intra-cranial 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 ACTH.

Clinical Trials

Data not 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 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%. 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 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*, *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

Contains: soya oil, glycerol, egg lecithin, oleic acid, sodium hydroxide and water for injections.

6.2 INCOMPATIBILITIES

Fresofol 1% should not be mixed prior to administration with injections or infusion solutions other than 5% glucose intravenous infusion solution, sodium chloride 0.9% intravenous infusion solution.

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

White, homogenous emulsion for intravenous infusion or injection containing propofol 10 mg per mL.

This product is supplied in:

20 mL (200 mg/20 mL propofol) in a colourless glass ampoule

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

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 1 x 50 mL glass vials
Packs containing 1 x 100 mL glass vials

Not all pack sizes may be marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

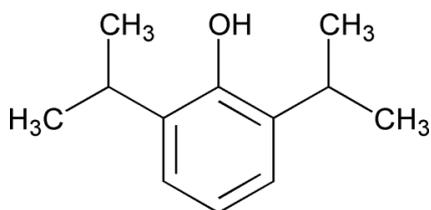
Unused portions of the injection as well as reservoirs, IV lines or solutions containing propofol injection, must be discarded at the end of the procedure or within 6 hours, whichever occurs sooner.

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

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

The chemical name of propofol is 2, 6-diisopropylphenol.



Molecular formula C₁₂H₁₈O

Molecular weight 178.27

CAS Number

2078-54-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: Schedule 4

New Zealand: Prescription Medicine

8 SPONSOR

Fresenius Kabi Australia Pty Limited

Level 2, 2 Woodland Way

Mount Kuring-gai NSW 2080

Australia

Tel: (02) 9391 5555

Fresenius Kabi New Zealand Limited

60 Pavillion Drive

Airport Oaks, Auckland

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Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

22 Mar 2005

10 Date of REVISION

07 Dec 2018

Summary table of changes

| Section changed | Summary of new information |
|------------------------|---|
| ALL | Reformat to the new TGA approved PI form |
| Section 4.4 | New warnings on the use of general anaesthetic agents and sedative medicines in pregnant women and young children |
| Section 4.8 | New warnings on the use of general anaesthetic agents and sedative medicines in pregnant women and young children |