PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

PROPOFOL 1 % PS FRESENIUS emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL emulsion contains 10 mg propofol.

Each 10 mL pre-filled syringe contains 100 mg propofol.

Each 20 mL pre-filled syringe contains 200 mg propofol.

Each 50 mL pre-filled syringe contains 500 mg propofol.

Excipients with known effect:

1 mL emulsion contains:

soya-bean oil, refined 50 mg

sodium, max. 0,06 mg

Contains sugar (as glycerol 22,5 mg/mL)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion in pre-filled syringe

White, homogeneous oil-in-water emulsion

pH of emulsion: 7,5 – 8,5

Osmolality of emulsion: 300 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROPOFOL 1 % PS FRESENIUS emulsion is a short-acting intravenous general anaesthetic for:

- The induction and maintenance of general anaesthesia, as part of a balanced anaesthetic technique.
- The sedation of ventilated adult patients receiving intensive care, for a period of up to 72 hours.
- Conscious sedation for surgical and diagnostic procedures in adults provided that there are adequate facilities for monitoring of haemodynamic and oxygenation parameters and if administered by a qualified anaesthetist.

4.2 Posology and method of administration

Supplementary analgesics are required in addition to PROPOFOL 1 % PS FRESENIUS, where analgesia is required.

Posology

A. ADULTS

Induction of general anaesthesia

PROPOFOL 1 % PS FRESENIUS may be used to induce anaesthesia by slow bolus injection or infusion.

In unpremedicated and premedicated patients:

Most adult patients aged less than 55 years are likely to require 1,5 mg/kg to 2,5 mg/kg (0,15 mL/kg - 0,25 mL/kg) of PROPOFOL 1 % PS FRESENIUS, (approximately 4 mL every 10 seconds in an average healthy adult) by slow bolus injection or infusion titrated against the

response of the patient until clinical signs show onset of anaesthesia. The total dose required can be reduced by lower rates of administration (20 mg/min - 50 mg/min [2 mL/min - 5 mL/min]).

Over the age of 55 years the requirement will generally be less. In patients of ASA (American Society of Anaesthesiologists) Grades 3 and 4, lower rates of administration should be used (approximately 20 mg [2 mL] every 10 seconds).

Maintenance of general anaesthesia

Anaesthesia can be maintained by administering PROPOFOL 1 % PS FRESENIUS either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia.

Infusion:

The average rate of administration varies between patients, but rates in the region of 4 mg/kg/h to 12 mg/kg/h (0,4 mL/kg/h – 1,2 mL/kg/h) usually maintain satisfactory anaesthesia. Slightly higher rates of administration may be required for 10 to 20 minutes after induction of anaesthesia.

Repeat bolus injections:

As a guide, increments of 25 mg (2,5 mL) to 50 mg (5,0 mL) may be used.

Sedation during intensive care

To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that PROPOFOL 1 % PS FRESENIUS should be given by continuous infusion, for up to 72 hours. Adjust infusion rate according to the depth of sedation required. Rates of 0,3 mg/kg/h to 4,0 mg/kg/h should achieve satisfactory sedation. Rates above 4,0 mg/kg/h are not recommended.

PROPOFOL 1 % PS FRESENIUS must not be used for sedation in intensive care of patients 16 years of age or younger.

Administration of propofol by a Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit (ICU).

Conscious sedation for surgical and diagnostic procedures *(see section 4.4)*

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 mg/kg to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating PROPOFOL 1 % PS FRESENIUS infusion to the desired level of sedation - most patients will require 1,5 mg/kg/h to 4,5 mg/kg/h. In addition to the infusion, bolus administration of 10 mg to 20 mg may be used if a rapid increase in the depth of sedation is required.

In patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

PROPOFOL 1 % PS FRESENIUS must not be used for conscious sedation for diagnostic and surgical procedures in patients of 16 years of age or younger.

B. ELDERLY PATIENTS

In elderly patients the dose requirement for induction of anaesthesia with PROPOFOL 1 % PS FRESENIUS is reduced. The reduction should consider the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response.

Where PROPOFOL 1 % PS FRESENIUS is used for maintenance of anaesthesia or sedation the rate of infusion or "target concentration" should also be reduced. Patients of

ASA Grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. CHILDREN

Induction of general anaesthesia

PROPOFOL 1 % PS FRESENIUS is not recommended for use in children less than 3 years of age (see sections 4.3 and 4.4).

It is recommended that PROPOFOL 1 % PS FRESENIUS be given slowly until the clinical signs show the onset of anaesthesia. Adjust dose for age and/or body weight. Most patients over 8 years of age are likely to require approximately 2,5 mg/kg (0,25 mL/kg) of PROPOFOL 1 % PS FRESENIUS for induction. Between the ages of 3 and 8 years the dose requirement may be higher. Lower dosage is recommended for children of ASA (American Society of Anesthesiologists) Grades 3 and 4.

Administration of PROPOFOL 1 % PS FRESENIUS by a TCI system is not advised for induction of general anaesthesia in children.

Maintenance of general anaesthesia

PROPOFOL 1 % PS FRESENIUS is not recommended for use in children less than 3 years of age (see section 4.3).

Administer PROPOFOL 1 % PS FRESENIUS by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients. 9 mg/kg/h to 15 mg/kg/hr (0,9 mL/kg/h - 1,5 mL/kg/h) usually achieves satisfactory anaesthesia.

Administration of PROPOFOL 1 % PS FRESENIUS by a Target Controlled Infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

Sedation during intensive care

PROPOFOL 1 % PS FRESENIUS is not recommended for sedation in children 16 years of age or younger, as safety and efficacy have not been demonstrated (see sections 4.3 and 4.4).

Administration of PROPOFOL 1 % PS FRESENIUS by a TCI system is not advised for sedation in the ICU.

Conscious sedation for surgical and diagnostic procedures

PROPOFOL 1 % PS FRESENIUS is not recommended for conscious sedation in children as safety and efficacy has not been demonstrated.

The duration of administration must not exceed 72 hours.

Method of administration

For intravenous use.

PROPOFOL 1 % PS FRESENIUS and any infusion equipment containing PROPOFOL 1 % PS FRESENIUS are for **single administration** in an **individual patient**. After use remaining solution of PROPOFOL 1 % FRESENIUS must be discarded.

Containers should be gently shaken before use.

PROPOFOL 1 % PS FRESENIUS should be inspected for particulate matter and discolouration before administration. Do not use if there is evidence of separation of the phases of the emulsion. Use only homogeneous preparations and undamaged containers.

General anaesthesia:

In accordance with established guidelines for other lipid emulsions a single infusion of PROPOFOL 1 % PS FRESENIUS must not exceed 6 hours. The syringe or giving set and any unused portion of PROPOFOL 1 % PS FRESENIUS or solution containing PROPOFOL 1 % PS FRESENIUS must be discarded at the end of the surgical procedure, or at 6 hours, whichever is the sooner, and replaced as appropriate.

Intensive care sedation:

Administration should commence promptly and must be completed within 12 hours after the syringe has been opened. The tubing and any unused portions of PROPOFOL 1 % PS FRESENIUS must be discarded after 12 hours.

If PROPOFOL 1 % PS FRESENIUS is transferred to another container prior to administration, the handling procedures for *"General anaesthesia*" (above) should be followed and the product should be discarded and administration lines changed after 6 hours.

When PROPOFOL 1 % PS FRESENIUS is used undiluted to maintain anaesthesia, it is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. PROPOFOL 1 % PS FRESENIUS can be used for infusion undiluted from plastic syringes.

PROPOFOL 1 % PS FRESENIUS can be diluted in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per mL) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation (see section 6.6).

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 PROPOFOL 1 % PS FRESENIUS. A burette, drop counter or volumetric pump must be

included in the infusion line. The risk of uncontrolled infusion must be considered when deciding the maximum amount of PROPOFOL 1 % PS FRESENIUS in the burette.
It is recommended that, when using diluted PROPOFOL 1 % PS FRESENIUS, the volume of the diluent removed from the infusion bag during the dilution process is totally replaced in volume by PROPOFOL 1 % PS FRESENIUS emulsion.
To reduce pain at the injection site, lidocaine (lignocaine) may be injected immediately before the use of PROPOFOL 1 % PS FRESENIUS or PROPOFOL 1 % PS FRESENIUS may be mixed, immediately before use, with preservative-free lidocaine (lignocaine) injection (20 parts of PROPOFOL 1 % PS FRESENIUS with up to 1 part of 1 % lidocaine (lignocaine) injection solution) under controlled and validated aseptic conditions. The mixture must be administered within 6 hours of preparation (see section 6.6). Dilutions with lidocaine (lignocaine) solution must not be used in patients with hereditary acute porphyria.
Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of PROPOFOL 1 % PS FRESENIUS.

4.3 Contraindications

- Known hypersensitivity to propofol or any of the excipients of PROPOFOL 1 % PS FRESENIUS (listed in section 6.1).
- PROPOFOL 1 % PS FRESENIUS contains soya oil and should not be used in patients who are hypersensitive to peanuts or soya.
- PROPOFOL 1 % PS FRESENIUS is not recommended for use in children less than 3 years of age.
- Sedation in children and adolescents 16 years of age and younger in intensive care (see section 4.4).

- Sedation of children of all ages with croup or epiglottitis receiving intensive care (see section 4.4).

4.4 Special warnings and precautions for use

PROPOFOL 1 % PS FRESENIUS should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in intensive care).

Respiration will be depressed and must be monitored to ensure adequate gas exchange.

Special care should be exercised when used with other respiratory depressants.

Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. PROPOFOL 1 % PS FRESENIUS should not be administered by the person conducting the diagnostic or surgical procedure.

A generalised systemic reaction which may be anaphylactic in nature (including angioedema, bronchospasm, erythema and hypotension) may occur following PROPOFOL 1 % PS FRESENIUS administration - estimated as 1 in 15 000.

Abuse of and dependence on PROPOFOL 1 % PS FRESENIUS, predominantly by healthcare professionals, have been reported. As with other general anaesthetics, the administration of PROPOFOL 1 % PS FRESENIUS without airway care may result in fatal respiratory complications.

When PROPOFOL 1 % PS FRESENIUS is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

When PROPOFOL 1 % PS FRESENIUS is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of PROPOFOL 1 % PS FRESENIUS. The use of PROPOFOL 1 % PS FRESENIUS may be associated with the development of a period of postoperative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

Propofol induced impairment is not generally detectable beyond 12 hours. The effects of PROPOFOL 1 % PS FRESENIUS, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other medicines that may sedate (e.g., benzodiazepines, opiates, alcohol.)

Interference with daily activities may continue for up to 24 hours and no legal/contractual decisions should be entered into for 24 hours after receiving anaesthetic/conscious sedation. Alcohol use should also be avoided for the same time period.

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When PROPOFOL 1 % PS FRESENIUS is combined with centrally depressant medicines administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that PROPOFOL 1 % PS FRESENIUS is administered following the analgesic and the dose should be carefully titrated to the patient's response (see section 4.5).

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other medicines.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of PROPOFOL 1 % PS FRESENIUS during the period of anaesthetic maintenance.

Special patient groups

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia

Caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. PROPOFOL 1 % PS FRESENIUS clearance is blood flow dependent, therefore, concomitant medicine that reduces cardiac output will also reduce PROPOFOL 1 % PS FRESENIUS clearance.

The pharmacokinetics of propofol may be prolonged in people with chronic hepatic cirrhosis or chronic renal impairment. Recovery times may double as a result. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.

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

PROPOFOL 1 % PS FRESENIUS should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.

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

The risk of relative vagotonia may be increased because PROPOFOL 1 % PS FRESENIUS lacks vagolytic activity. It has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic medicine before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when PROPOFOL 1 % PS

FRESENIUS is used in conjunction with other medicines likely to cause a bradycardia.

Routine premedication with anticholinergic medicines is not advised.

Epilepsy

When PROPOFOL 1 % PS FRESENIUS is administered to an epileptic patient, there may be a risk of convulsion. PROPOFOL 1 % PS FRESENIUS should therefore be used with caution in patients with epilepsy.

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

Before anaesthesia of an epileptic patient, it should be checked that the patient has received antiepileptic treatment. Although several studies have demonstrated efficacy in treating status epilepticus, administration of PROPOFOL 1 % PS FRESENIUS in epileptic patients may also increase the risk of seizure.

Use of PROPOFOL 1 % PS FRESENIUS is not recommended with electroconvulsive treatment.

Paediatric population

PROPOFOL 1 % PS FRESENIUS is contraindicated in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

PROPOFOL 1 % PS FRESENIUS is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes (see section 4.3).

PROPOFOL 1 % PS FRESENIUS must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).
Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections, given doses in excess of those recommended for adults. Associated findings include metabolic acidosis, lipaemia, rhabdomyolysis, cardiac irregularities and renal failure.

Patients with disorders of fat metabolism

Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed to fat embolism and in other conditions where lipid emulsions must be used cautiously. Lipids should be monitored in the Intensive Care Unit treatment after 3 days.
Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolic disorders, severe trauma including long-bone and multiple fractures, and sepsis.
Blood lipid levels should be monitored if PROPOFOL 1 % PS FRESENIUS is administered to patients thought to be at particular risk of fat overload. Administration of PROPOFOL 1 % PS FRESENIUS should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation. 1,0 mL of PROPOFOL 1 % PS FRESENIUS contains approximately 0,1 g of fat.

Patients with high intracranial pressure

Special care and close monitoring should be exercised in patients with a high intracranial pressure and a low mean arterial pressure as there is a risk of a significant decrease of the intracerebral pressure.

Mitochondrial disease

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the “propofol infusion syndrome” may be similar.

Advisory statements concerning ICU management (Propofol infusion syndrome)

Use of PROPOFOL 1 % PS FRESENIUS emulsion infusions for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death.

Reports have been received of combinations of the following:

Metabolic acidosis, rhabdomyolysis, hyperkalaemia, hepatomegaly, renal failure, hyperlipidaemia, cardiac dysrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive cardiac failure usually unresponsive to inotropic supportive treatment (see section 4.8).

Combinations of these events have been referred to as the “propofol infusion syndrome”.

These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the ICU.

The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following medicines - vasoconstrictors, steroids, inotropes and/or PROPOFOL 1 % PS FRESENIUS (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue PROPOFOL 1 % PS FRESENIUS when the above signs develop.

All sedative and therapeutic medicines used in the ICU, should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intracranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Treating medical practitioners are reminded, if possible, not to exceed the dosage of 4 mg/kg/h.

Information on some of the ingredients

PROPOFOL 1 % PS FRESENIUS contains soybean oil, which may cause severe allergic reaction in some cases. PROPOFOL 1 % PS FRESENIUS should not be used in patients with an allergy to peanuts, eggs, or soya protein (see section 4.3).

PROPOFOL 1 % PS FRESENIUS contains less than 1 mmol (23 mg) sodium per 100 mL, i.e., essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

PROPOFOL 1 % PS FRESENIUS has been used in association with spinal and epidural anaesthesia and with commonly used premedications, neuromuscular blocking medicines, inhalational medicines and analgesic medicines; no pharmacological incompatibility has

been encountered. Dosage adjustment may be necessary when used together with the above medicines, particularly the narcotics (e.g., morphine, meperidine and fentanyl), combinations of opioids and sedatives (e.g., benzodiazepines, barbiturates, droperidol etc.), supplementary analgesic medicines (e.g., nitrous oxide or opioids) and the potent inhalation medicines (e.g., isoflurane, enflurane and halothane).

Lower doses of PROPOFOL 1 % PS FRESENIUS may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.

Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

The concurrent administration of other central nervous system (CNS) depressants such as premedications, inhalation medicines, analgesics, sedatives such as benzodiazepines, opiates, alcohol, may add to the sedative, anaesthetic and cardiorespiratory depressant effects of PROPOFOL 1 % PS FRESENIUS (see section 4.4).

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

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

Leukoencephalopathy has been reported with administration of lipid emulsions such as PROPOFOL 1 % PS FRESENIUS in patients receiving ciclosporin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

PROPOFOL 1 % PS FRESENIUS should not be used in pregnancy. PROPOFOL 1 % PS FRESENIUS crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia. PROPOFOL 1 % PS FRESENIUS has been used, however, during termination of pregnancy in the first trimester.

Breastfeeding

In mothers who are breastfeeding, safety to the neonate has not been established. Women should therefore not breastfeed for 24 hours after administration of PROPOFOL 1 % PS FRESENIUS. Milk produced during this period should be discarded.

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.

After administration of PROPOFOL 1 % PS FRESENIUS, the patient should be kept under observation for an appropriate period of time. The patient should be instructed not to drive, operate machinery, or work in potentially hazardous situations. The patient should not be allowed to go home unaccompanied and should be instructed to avoid consumption of alcohol.

Propofol induced impairment is not generally detectable beyond 12 hours (see section 4.4).

4.8 Undesirable effects

a. Summary of the safety profile

Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation. The most frequently reported adverse reactions are pharmacologically predictable side effects of an anaesthetic/sedative medicine, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving propofol may

be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

b. Tabulated list of adverse reactions

SYSTEM ORGAN CLASS/ *FREQUENCY*	**ADVERSE REACTION**
Immune system disorders:	
Less frequent:	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutritional disorder:	
Frequency not known[9]*:*	Metabolic acidosis[5], hyperkalaemia[5], hyperlipidaemia[5]
Psychiatric disorders:	
Frequency not known[9]:	Euphoric mood, sexual disinhibition, medicine abuse and dependence[8]
Nervous system disorders:	
Frequent:	Headache during recovery phase
Less frequent:	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery, vertigo, shivering and sensation of cold during recovery, postoperative unconsciousness
Frequency not known[9]*:*	Involuntary movements
Cardiac disorders:	
Frequent:	Bradycardia[1] and tachycardia during induction
Less frequent:	Pulmonary oedema
Frequency not known[9]:	Cardiac dysrhythmia[5], cardiac failure[5,7]
Vascular disorders:	

Frequent: Hypotension[2]

Less frequent: Thrombosis and phlebitis

Respiratory, thoracic and mediastinal disorders:

Frequent: Transient apnoea, coughing, singultus during induction

Frequency not known[9]: Respiratory depression (dose dependant)

Gastrointestinal disorders:

Frequent: Nausea and vomiting during recovery phase

Less frequent: Pancreatitis

Hepatobiliary disorders

Frequency not known[9]: Hepatomegaly[5]

Musculoskeletal and connective tissue disorders:

Frequency not known[9]: Rhabdomyolysis[3,5]

Renal and urinary disorders:

Less frequent: Discolouration of urine following prolonged administration

Frequency not known[9]: Renal failure[5]

Reproductive system and breast disorders:

Frequency not known[9]: Priapism

General disorders and administration site conditions:

Frequent: Local pain on induction[4]

Less frequent: Tissue necrosis[10] following accidental extravascular administration

Frequency not known[9]: Local pain, swelling, following accidental extravascular administration

Investigations:

Frequency not known[9]: Brugada-type ECG[5,6]

Injury, poisoning and procedural complications:

Less frequent:	Postoperative fever

(1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of propofol.

(3) Reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/h for ICU sedation.

(4) May be minimised by using the larger veins of the forearm and antecubital fossa. Local pain can also be minimised by the injection of lidocaine (lignocaine) immediately before the use of PROPOFOL 1 % PS FRESENIUS (see section 4.2 - Method of administration).

(5) Combinations of these events, reported as “Propofol infusion syndrome”, may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4.

(6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.

(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

(8) Abuse of propofol and dependence on propofol, predominantly by healthcare professionals.

(9) Not known as it cannot be estimated from the available clinical trial data.

(10) Necrosis has been reported where tissue viability has been impaired.

Dystonia/dyskinesia have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Accidental overdosage is likely to cause cardiorespiratory depression.

Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of the patient's head and, if severe, use of plasma expanders and pressor substances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics; Other general anaesthetics

ATC-Code: N01AX10

Category and class: A.2.1 Anaesthetics

Mechanism of action

Propofol (2,6-di-isopropylphenol) is a short-acting sedative hypnotic with a rapid onset of action of approximately 30 seconds. The mechanism of action is poorly understood.

Pharmacodynamic effects

Falls in mean arterial blood pressure and changes in heartrate are observed when propofol is administered.

Ventilatory depression can occur following administration of propofol.

Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism.

Clinical efficacy and safety

Recovery from anaesthesia is usually rapid and clear-headed.

Propofol has an anti-emetic effect.

Propofol, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 Pharmacokinetic properties

Absorption

The decline in propofol concentrations following the termination of an infusion can be described by a 3-compartment open model.

The first phase is characterised by a rapid distribution (half-life: 2 to 4 minutes) followed by rapid elimination (half-life: 30 to 60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Distribution/Biotransformation/Elimination

Propofol is bound to plasma proteins for 98 %.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance: 1,5 – 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

The pharmacokinetics are linear over the recommended range of infusion rates of propofol.

Under the usual maintenance regimens, significant accumulation of propofol does not occur.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined

Medium-chain triglycerides

Purified egg phosphatides

Glycerol

Oleic acid

Sodium hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

PROPOFOL 1 % PS FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

Muscle relaxants like atracurium and mivacurium should not be administered through the same intravenous line as PROPOFOL 1 % PS FRESENIUS without prior flushing.

6.3 Shelf life

Shelf life in original package before opening: 24 months.

Shelf life after first opening: PROPOFOL 1 % PS FRESENIUS must be used immediately after first opening.

Administration systems with undiluted PROPOFOL 1 % PS FRESENIUS should be replaced after 12 hours.

Shelf life after dilution: PROPOFOL 1 % PS FRESENIUS must be used immediately after dilution. The administration should be completed within 6 hours after dilution.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

6.5 Nature and contents of container

10 mL, 20 mL, 50 mL pre-filled syringe (cyclo-olefin-copolymer) with bromobutyl tip cap, bromobutyl plunger and PP piston rod

10 mL, 20 mL pre-filled syringe (glass, hydrolytic class 1) with bromobutyl tip cap, bromobutyl plunger and PP piston rod

Packs containing 6 plastic syringes with 10 mL emulsion

Packs containing 5 glass syringes with 10 mL emulsion

Packs containing 6 plastic syringes with 20 mL emulsion

Packs containing 5 glass syringes with 20 mL emulsion

Packs containing 1 plastic syringe with 50 mL emulsion

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When PROPOFOL 1 % PS FRESENIUS is to be aspirated, it must be drawn aseptically into a giving set immediately after opening the syringe. Administration must commence without delay.

Asepsis must be maintained for both PROPOFOL 1 % PS FRESENIUS and infusion equipment throughout the infusion period. Any infusion fluids added to the PROPOFOL 1 % PS FRESENIUS infusion line must be administered close to the cannula site.

PROPOFOL 1 % PS FRESENIUS must not be administered via a microbiological filter.

PROPOFOL 1 % PS FRESENIUS should not be mixed prior to administration with injection or infusion solutions other than glucose (dextrose) 50 mg/mL (5 %) solution for injection, sodium chloride 9 mg/mL (0,9 %) solution for injection, preservative free lidocaine (lignocaine) 10 mg/mL (1 %) solution for injection or alfentanil injection. The maximum dilution must not exceed 1 part of PROPOFOL 1 % PS FRESENIUS with 4 parts of glucose 50 mg/mL (5 %) solution for injection or sodium chloride 9 mg/mL (0,9 %) solution for injection (minimum propofol concentration: 2 mg/mL).

The mixture should be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 6 hours after preparation (see also section 4.2).

Any unused emulsion must be discarded. PROPOFOL 1 % PS FRESENIUS contains no antimicrobial preservatives, and the vehicle supports growth of microorganisms.

Final propofol concentration must not be below 2 mg/mL.

Co-administration of a glucose 50 mg/mL (5 %) solution for injection or sodium chloride 9 mg/mL (0,9 %) solution for injection or sodium chloride 1,8 mg/mL (0,18 %) solution for injection and glucose 40 mg/mL (4 %) solution for injection with PROPOFOL 1% PS FRESENIUS is permitted via a Y-piece connector close to the injection site.

Application of pre-filled syringes (for pre-assembled syringes step 2 can be omitted)

Sterility has to be ensured. The outer surface of the syringe and plunger rod are not sterile.

1) Take out the syringe from the packaging and shake it.

2) Insert the plunger rod by screwing it clockwise into the syringe.

3) Remove the tip-cap from the syringe and connect the infusion line, needle or cannula to the syringe. Get rid of the air bubble (a small bubble can remain) and the ready -to-use syringe will be installed in the pump or administered manually.

Administration by TCI in adults:

PROPOFOL 1 % PS FRESENIUS (**20 mL and 50 mL plastic syringes only**) may also be used by a TCI system for induction and maintenance of general anaesthesia in adults. Due to the different algorithms available on the market for dosage recommendations please refer to the instructions for use leaflet of the device manufacturer. Administration of PROPOFOL 1 % PS FRESENIUS via a TCI system is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street, Halfway House extension 7

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South Africa

8. REGISTRATION NUMBER

49/2.1/1233

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2021

10. DATE OF REVISION OF THE TEXT

17 July 2024