**PACKAGE INSERT - INSTRUCTIONS FOR USE - READ CAREFULLY!**

# Propofol 1% Fresenius

## emulsion for injection or infusion

**Composition**

1 ml emulsion contains 10 mg propofol.
Each 20 ml ampoule contains 200 mg propofol.
Each 50 ml vial contains 500 mg propofol.
Each 100 ml vial contains 1000 mg propofol.

Also contains soya-bean oil, refined, purified egg phosphatides, glycerol, oleic acid, sodium hydroxide, water for injections.

| 1 ml emulsion contains | |
|---|---|
| soya-bean oil, refined | 100 mg |
| sodium | max. 0.06 mg |

**Pharmaceutical form**

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

**Address of the pharmaceutical company**

Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Germany

Manufacturers:

Fresenius Kabi Austria GmbH
Hafnerstraße 36
A-8055 Graz
Austria

Fresenius Kabi AB
Rapsgatan 7
S-75174 Uppsala
Sweden

**Therapeutic indications**

Propofol 1% Fresenius is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children > 1 month
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 1 month
- sedation of ventilated patients > 16 years of age in the intensive care unit

**Contraindications**

Propofol 1% Fresenius must not be used

- in patients with a known hypersensitivity to propofol, soya, peanut or to any of the excipients of the emulsion.
- in patients who are allergic to soya or peanut.
- in patients of 16 years of age or younger for sedation in intensive care.

**Pregnancy and lactation**

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

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

**Special warnings and precautions for use**

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. **Propofol clearance is blood flow dependent, therefore, concomitant medication which reduces cardiac output will also reduce propofol clearance.**

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of Propofol 1% Fresenius.

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

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

The risk of relative vagotonia may be increased because propofol lacks vagolytic activity. It has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia with Propofol 1% Fresenius should be considered, especially in situations where vagal tone is likely to predominate or when Propofol 1% Fresenius is used in conjunction with other agents likely to cause a bradycardia.

Use of Propofol 1% Fresenius is not recommended with electroconvulsive therapy.

As with other sedative agents, when propofol is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

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

Lipids should be monitored in the Intensive Care Unit treatment every 2 days.

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

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

To reduce pain on the injection site during induction of anaesthesia with Propofol 1% Fresenius, lidocaine can be injected prior to the propofol emulsion. Lidocaine must not be used in patients with hereditary acute porphyria.

Propofol 1% Fresenius is not advised for general anaesthesia in children younger than 1 month of age.

Administration of Propofol 1% Fresenius by a target controlled infusion (TCI) system is not advised for the use in children.

In any case, special care should be exercised when propofol is used for anaesthesia in infants and children up to 3 years of age, although currently available data do not suggest significant differences in terms of safety compared with children older than 3 years.

The safety of propofol for (background) sedation in the intensive care unit in children and adolescents younger than 16 years of age has 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, renal failure 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 ICU.

Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia, arrhythmias and/or rapidly progressive cardiac failure (in some cases with fatal outcome) in adults who were treated for more than 48 hours with dosages in excess of 5 mg propofol/kg bodyweight/h. This exceeds the maximum dosage of 4 mg propofol/kg bodyweight/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with increased intracranial pressure (ICP). The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment. Treating physicians are reminded if possible not to exceed the dosage of 4 mg propofol/kg bodyweight/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the propofol dosage or switching to an alternative sedative at the first sign of occurrence of respective symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

The use of Propofol 1% Fresenius is not recommended for newborn infants as this patient population has not been fully investigated. Pharmacokinetic data indicate that clearance is considerably reduced in neonates with a very high inter-individual variability. Relative overdose could occur administering doses recommended for older children resulting in severe cardiovascular depression.

In isolated cases there may be a phase of postoperative unconsciousness that may be accompanied by an increased muscular tone. The appearance of this period is not dependent whether the patient came out of an anaesthetic or not. Although consciousness is spontaneously regained the unconscious patient should be kept under intensive observation.

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

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

**Effects on ability to drive and use machines**

After administration of Propofol 1% 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.

**Interactions with other medicinal products and other forms of interaction**

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

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

Concomitant use of benzodiazepines, parasympatholytic agents or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

After additional premedication with opioids, the sedative effects of propofol may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea.

It should be taken into consideration that concomitant use of propofol and medicinal products for premedication, inhalation agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects. Concomitant use of central nervous system depressants (e.g. alcohol, general anaesthetics, narcotic analgesics) will result in intensification of their sedative effects. When Propofol 1% Fresenius is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur.

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

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

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

**Incompatibilities**

Propofol 1% Fresenius should not be mixed prior to administration with injection or infusion solutions other than 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 1% preservative free lidocaine injection solution (see also section “Posology and method of administration”). Final propofol concentration must not be below 2 mg/ml.

**Posology and method of administration**

Propofol 1% Fresenius must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care.

Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse oxymetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.

For sedation during surgical and diagnostic procedures Propofol 1% Fresenius should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Propofol 1% Fresenius emulsion should be individualised based on the response of the patient and premedications used.

Supplementary analgesic agents are generally required in addition to Propofol 1% Fresenius.

**Posology**

***General anaesthesia in adults***

Induction of anaesthesia:

For induction of anaesthesia Propofol 1% Fresenius should be titrated (approximately 20 - 40 mg propofol every 10 seconds) against the response of the patient until clinical signs show the onset of anaesthesia.

Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg propofol/kg bodyweight.

In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Propofol 1% Fresenius may be reduced to a minimum of 1 mg propofol/kg bodyweight. Lower rates of administration of Propofol 1% Fresenius should be used (approximately 2 ml (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 1% Fresenius either by continuous infusion or repeat bolus injections.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg bodyweight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg bodyweight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

In elderly patients, patients in unstable general conditions, patients with impaired cardiac function or hypovolaemic patients and patients of ASA grades III and IV the dosage of Propofol 1% Fresenius may be reduced further depending on the severity of the patient’s condition and on the performed anaesthetic technique.

For maintenance of anaesthesia using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 - 5 ml Propofol 1% Fresenius) should be given according to clinical requirements.

Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiopulmonary depression.

***General anaesthesia in children over 1 month of age***

Induction of anaesthesia:

For induction of anaesthesia Propofol 1% Fresenius should be titrated slowly until clinical signs show the onset of anaesthesia. The dose should be adjusted according to age and/or bodyweight. Most patients over 8 years of age require approximately 2.5 mg/kg bodyweight Propofol 1% Fresenius for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5 – 4 mg/kg bodyweight).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering Propofol 1% Fresenius by infusion or repeated bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9-15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA III and IV patients lower doses are recommended (see also section “Special warnings and precautions for use”).

***Sedation for diagnostic and surgical procedures in adult patients***

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 - 1 mg propofol/kg bodyweight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% Fresenius infusion to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg bodyweight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg propofol (1 – 2 ml Propofol

1% Fresenius) if a rapid increase of the depth of sedation is required.

In patients older than 55 years and in patients of ASA grades III and IV lower doses of Propofol 1% Fresenius may be required and the rate of administration may need to be reduced.

***Sedation for diagnostic and surgical procedures in children over 1 month of age***

Doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1 – 2 mg/kg bodyweight propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% Fresenius infusion to the desired level of sedation. Most patients require 1.5 – 9 mg/kg/h propofol. The infusion may be supplemented by bolus administration of up to 1 mg/kg bodyweight if a rapid increase of depth of sedation is required.

In ASA III and IV patients lower doses may be required.

***Sedation in patients over 16 years of age in the intensive care unit***

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol 1% Fresenius should be given by continuous infusion. The dose should be adjusted according to the depth of sedation required. Usually satisfactory sedation is achieved with administration rates in the range of 0.3 to 4.0 mg propofol/kg bodyweight/h. Rates of infusion greater than 4.0 mg propofol/kg bodyweight/h are not recommended (see section "Special warnings and precautions for use").

Administration of Propofol 1% Fresenius by a target controlled infusion (TCI) system is not advised for sedation in the intensive care unit (ICU).

**Method of administration**

For intravenous use.

Propofol 1% Fresenius can be used for infusion undiluted or diluted with 5% w/v glucose intravenous infusion solution or 0.9% w/v sodium chloride intravenous infusion solution only, in glass infusion bottles.

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

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

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

Propofol 1% Fresenius is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of micro-organisms.

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

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

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

Propofol 1% Fresenius must not be administered via a microbiological filter.

Propofol 1% Fresenius and any infusion equipment containing Propofol 1% Fresenius are for ***single*** administration in an ***individual*** patient. After use remaining solution of Propofol 1% Fresenius has to be discarded.

Infusion of undiluted Propofol 1% Fresenius:

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

Infusion of diluted Propofol 1% Fresenius:

For administering infusion of diluted Propofol 1% Fresenius, burettes, drop counters 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 Propofol 1% Fresenius. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

The maximum dilution must not exceed 1 part of Propofol 1% Fresenius with 4 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration 2 mg propofol per 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.

Propofol 1% Fresenius must not be mixed with other solutions for infusion or injection. However, co-administration of a 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 0.18% w/v sodium chloride and 4% w/v glucose solution with Propofol 1% Fresenius is permitted via a Y-piece connector close to the injection site.

To reduce pain on the injection site, lidocaine may be injected immediately before the use of Propofol 1% Fresenius (see section "Special warnings and precautions for use"). Alternatively, Propofol 1% Fresenius may be mixed, immediately for use, with preservative free lidocaine injection (20 parts of Propofol 1% Fresenius with up to 1 part of 1% lidocaine injection solution) under controlled and validated aseptical conditions. The mixture has to be administered within 6 hours after preparation.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Propofol 1% Fresenius.

**Duration of administration**

The duration of administration must not exceed 7 days.

**Overdose**

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

**Undesirable effects**

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

In this section undesirable effects are defined as follows:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

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

*Immune system disorders:*

Rare:
Clinical features of anaphylaxis, which may include angiooedema, bronchospasm, erythema and hypotension.

Very rare:
Allergic reactions caused by soya-bean oil.

*Metabolism and nutrition disorders:*

Common:
Hypertriglyceridemia.

*Psychiatric disorders:*

Rare:
Euphoria, sexual phantasies and sexual disinhibition during the recovery period.

*Nervous system disorders:*

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

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

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

*Cardiac disorders / Vascular disorders:*

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

Uncommon:
Marked hypotension. This may require a lowering of the administration rate of Propofol 1% Fresenius and/or fluid replacement therapy, if necessary vasoconstrictive medicinal products. Account should be taken of the possibility of a severe drop in blood pressure in patients with impaired coronary or cerebral perfusion or those with hypovolaemia.
Bradycardia during general anaesthesia with progressive severity (asystole). The intravenous administration of an anticholinergic medicinal product prior to induction or during maintenance of anaesthesia should be considered (see also section "Special warnings and precautions for use").

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

*Respiratory, thoracic and mediastinal disorders:*

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

Uncommon:
Coughing during maintenance of anaesthesia.

Rare:
Coughing during the recovery period.

Very rare:
Pulmonary oedema.

*Gastrointestinal disorders:*

Rare:
Nausea or vomiting during the recovery period.

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

*Skin and subcutaneous tissue disorders:*

Very rare:
Severe tissue responses after accidental paravenous application.

*Renal and urinary disorders*:

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

*General disorders and administration site conditions:*

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

The local pain which may occur during the initial injection of Propofol 1% Fresenius can be minimised by the co-administration of lidocaine (see section "Method of administration", section "Infusion of diluted Propofol 1% Fresenius") and by injection or infusion into the larger veins of the forearm and antecubital fossa. Upon co-administration of lidocaine the following undesirable effects may occur rarely (≥1/10,000 to <1/1,000): giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

Rare:
Cases of post-operative fever

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

**Pharmaceutical precautions**

Keep out of the reach and sight of children.

Do not use Propofol 1% Fresenius after the expiry date which is stated on the ampoule/vial and the outer packaging after EXP. The expiry date refers to the last day of that month.

Containers should be shaken before use.
If two layers can be seen after shaking the emulsion should not be used.
Use only homogeneous preparations and undamaged containers.
Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol.
After use, tapped containers must be discarded.
After opening the product must be used immediately.

Administration systems with undiluted Propofol 1% Fresenius should be replaced after 12 hours.

Dilutions with 5% w/v glucose solution or 0.9% w/v sodium chloride solution or an admixture with 1% preservative free lidocaine injection solution (at least 2 mg propofol per ml) should be prepared aseptically (controlled and validated conditions preserved) immediately before administration and administration should be completed within 6 hours after dilution.

For single use. Any unused emulsion must be discarded.

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

**Presentation**

5 glass ampoules with 20 ml emulsion
1, 10 and 15 glass vials with 50 ml emulsion
1, 10 and 15 glass vials with 100 ml emulsion

Not all pack sizes may be marketed.

**Revision date**
November 2010

FRESENIUS KABI