1.6.3 Package insert

SCHEDULING STATUS

S5

PROPRIETARY NAMES AND DOSAGE FORM

Fresenius Propoven 1 % (20 ml) Emulsion for injection or Infusion
Fresenius Propoven 1 % (50 ml) Emulsion for injection or Infusion
Fresenius Propoven 1 % (100 ml) Emulsion for injection or Infusion

COMPOSITION

1 ml emulsion contains 10 mg propofol.
Each 20 ml ampoule/vial contains 200 mg propofol
Each 50 ml vial contains 500 mg propofol
Each 100 ml vial contains 1 000 mg propofol
Excipients:
Soya bean oil
Medium chain triglycerides
Purified egg phosphatides
Glycerols
Oleic acid
Sodium hydroxide
Water for injection
Contains sugar (as Glycerol)

PHARMACOLOGICAL CLASSIFICATION

A 2.1 Anaesthetics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 – 6 minutes).With the recommended dosage schedule, a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalizes during maintenance of anaesthesia.

Pharmacokinetic properties

After intravenous administration about 98 % of propofol is bound to plasma protein. After intravenous bolus administration, the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α-phase). The distribution half-life has been calculated as 2 – 4 minutes. During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 – 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

Clearance is higher in children than adults.

The central volume of distribution is in the range of 0,2 – 0,79 l/kg body weight, the steady-state volume of distribution in the range of 1,8 – 5,3 l/kg body weight. Propofol is rapidly cleared from the body (total clearance 1,5 – 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive. About 88 % of an administered dose is excreted in the form of metabolites in urine. Only 0,3 % of the administered dose is excreted unchanged in urine.

INDICATIONS

Fresenius Propoven 1 % is a short-acting intravenous general anaesthetic agent for:

- Induction and maintenance of general anaesthesia.
- Sedation of artificially ventilated patients in the Intensive Care Unit (ICU) for 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.

CONTRA-INDICATIONS

Fresenius Propoven 1 % must not be used:

- in patients with a known hypersensitivity to propofol or to any of the excipients
- in patients who are allergic to soya or peanut
- for sedation in children 16 years of age and younger

WARNINGS AND SPECIAL PRECAUTIONS

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

Use is not recommended with electroconvulsive therapy.In patients with cardiac, respiratory, renal or hepatic impairment or in elderly, debilitated, hypovolemic or epileptic patients or patients with disorders of consciousness Fresenius Propoven 1 % should be administered with caution and a reduced administration rate. Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of Fresenius Propoven 1 %.The risk of relative vagotonia may be increased because Fresenius Propoven 1 % lacks vagolytic activity. It has been associated with reports of bradycardia 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 Fresenius Propoven 1 % is used in conjunction with other agents likely to cause a bradycardia.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 Fresenius Propoven 1 % in epileptic patients may also increase the risk of seizure.When Fresenius Propoven 1 % is used for sedation during operative procedures, involuntary patient movements may occur. 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 Fresenius Propoven 1 % formulation. 1,0 ml of Fresenius Propoven 1 % contains 0,1 g of fat. Lipids should be monitored in the Intensive Care Unit treatment after 3 days.

Due to a higher dosage in patients with severe obesity the risk of haemodynamic effects on the cardiovascular system should be taken into consideration.Special care should be recognized 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.Dilutions with lidocaine solution must not be used in patients with hereditary acute porphyria.The safety of Fresenius Propoven 1 % for sedation in children younger than 16 years of age has not been demonstrated. Serious undesirable effects with sedation in patients younger than 16 years of age have been reported during unlicensed use. In particular these effects concerned metabolic acidosis, hyperlipidaemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation. Similarly reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure in adults treated for more than 58 hours with dosages in excess of 5 mg Fresenius Propoven 1 %/kg body weight/h. Treating physicians are reminded not to exceed the dosage of 4 mg Fresenius Propoven 1 %/kg body weight/h. Prescribers should consider decreasing the Fresenius Propoven 1 % dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Although consciousness returns spontaneously, unconscious patients should be kept under close observation.Fresenius Propoven 1 % contains soybean oil, which might cause severe allergic reactions.

INTERACTIONS

Fresenius Propoven 1 % can be used in combination with other medicinal products for anaesthesia (premedication, 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 Fresenius Propoven 1 %. 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 Fresenius Propoven 1 % may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea. Use of Fresenius Propoven 1 % with medicines used for premedication, inhalation agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects. When used with centrally depressant agents administered parenterally, severe respiratory and cardiovascular depression may occur. After administration of fentanyl, the blood level of Fresenius Propoven 1 % 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 Fresenius Propoven 1 % in patients receiving cyclosporine.

HUMAN REPRODUCTION

The safety of Fresenius Propoven 1 % during pregnancy has not been established. Fresenius Propoven 1 % crosses the placenta and may be associated with neonatal depression. Fresenius Propoven 1 % is excreted in small amounts into the milk. Therefore, mothers should stop breast-feeding and discard breast milk for 24 hours after administration of Fresenius Propoven 1 %.

DOSAGE AND DIRECTIONS FOR USE

Fresenius Propoven 1 % 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 and facilities for maintenance of patient airways, artificial

ventilation and other resuscitation facilities should be immediately available at all times. The dose of Fresenius Propoven 1 % emulsion should be individualized based on the response of the patient and premedication used. Supplementary analgesic agents are generally required in addition to Fresenius Propoven 1 %.

General anaesthesia in adults:

Induction of anaesthesia:

For induction of anaesthesia Fresenius Propoven 1 % should be titrated (± 20 – 40 mg Fresenius Propoven 1 % 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 Fresenius Propoven 1 %/kg body weight. In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Fresenius Propoven 1 % may be reduced to a minimum of 1 mg/kg body weight. Lower rates of administration of Fresenius Propoven 1 % should be used (± 2 ml (20 mg Fresenius Propoven 1 %) every 10 seconds).

Maintenance of anaesthesia:

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

For maintenance of anaesthesia generally doses of 4 – 12 mg Fresenius Propoven 1 % /kg body weight/h should be given. A reduced maintenance dose of ± 4 mg Fresenius Propoven 1 % /kg body weight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery. In elderly patients, patients in unstable general conditions, patients with impaired cardiac function or hypovolaemic patients and patients of ASA grades III and IV, the dosage of Fresenius Propoven 1 % 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 Fresenius Propoven 1 % (= 2,5 – 5 ml Fresenius Propoven 1 %) 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:

Induction of anaesthesia:

Fresenius Propoven 1 % should be titrated slowly until the clinical signs show the onset of anaesthesia. The dosage should be adjusted for age and/or body weight. Children over 8 years of age are likely to require ± 2,5 mg Fresenius Propoven 1 %/kg body weight for induction of anaesthesia. Under this age the dose requirement may be higher. The initial dose should be 3 mg Fresenius Propoven 1 % /kg body weight. If necessary, additional doses in steps of 1 mg Fresenius Propoven 1 %/kg body weight can be administered. Lower doses are recommended for young patients at increased risk (ASA grades III and IV). Administration of Fresenius Propoven 1 % by a Target Controlled Infusion (TCI) system is not advised for induction of general anaesthesia in children.

Maintenance of anaesthesia:

For maintenance of anaesthesia using continuous infusion doses of 9 – 15 mg Fresenius Propoven 1 %/kg body weight/h should be given. Younger children may need higher dosage requirements, within the range of recommended dosages, when compared with older paediatric patients. There is no data on maintenance of anaesthesia with repeated injections of Fresenius Propoven 1 % in children.

Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia. A maximum duration of use of ± 60 minutes should not be exceeded except where there is a specific indication for longer use e.g. malignant hyperthermia where volatile agents must be avoided. Administration of Fresenius Propoven 1 % by a Target Controlled Infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

Sedation in adults during intensive care:

When used to provide sedation during intensive care, it is recommended that Fresenius Propoven 1 % 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 Fresenius Propoven 1 %/kg body weight/h. Rates of infusion greater than 4 mg Fresenius Propoven 1 %/kg body weight/h are not recommended.

Fresenius Propoven 1 % must not be used for sedation in intensive care of patients 16 years of age or younger.

Administration of Fresenius Propoven 1 % by a Target Controlled Infusion (TCI) system is not advised for sedation in the Intensive Care Unit.

Conscious sedation for surgical and diagnostic procedures:

To provide sedation for surgical and diagnostic procedures rates of administration should be individualized and titrated to clinical response. Most patients will require 0,5 – 1 mg/kg over 1 to 5 minutes to initiate sedation. Maintenance of sedation may be accomplished by titrating Fresenius Propoven 1 % to the desired level of sedation – most patients will require 1,5 to 4,5 mg/kg/hr. 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 patient in ASA grades 3 and 4 the rate of administration and dosage may need to be reduced. **Fresenius Propoven 1 % must not be used for sedation for diagnostic and surgical procedures in patients of 16 years of age or younger.**

Method of administration:

For intravenous use. Fresenius Propoven 1 % can be used for infusion undiluted or diluted with Dextrose 5 % intravenous infusion solution or Sodium chloride 0,9 % intravenous infusion solution only, in glass infusion bottles. 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.

Fresenius Propoven 1 % is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of microorganisms. 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 Fresenius Propoven 1 % and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Fresenius Propoven 1 % infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve. Fresenius Propoven 1 % must not be mixed with other solutions for infusion or injection. But 5 % *m/v* glucose solution, 0,9 % *m/v* sodium chloride solution or 0,18 % *m/v* sodium chloride and 4 % *m/v* glucose solution may be administered via suitable appendages at the cannula site. Fresenius Propoven 1 % must not be administered via a microbiological filter. Fresenius Propoven 1 % and any infusion equipment containing Fresenius Propoven 1 % are for single administration in an individual patient. After use remaining solution of Fresenius Propoven 1 % must be discarded.

Infusion of undiluted Fresenius Propoven 1 %:

When Fresenius Propoven 1 % is infused undiluted, it is recommended that equipment such as burettes, drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. As usual for fat emulsions, the infusion of Fresenius Propoven 1 % via one infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Fresenius Propoven 1 % must be discarded or replaced if necessary.

Infusion of diluted Fresenius Propoven 1 %:

When Fresenius Propoven 1 % is infused diluted, it is recommended that equipment such as 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 Fresenius Propoven 1 %. This risk must be

taken into account when the decision for the maximum dilution in the burette is made. The maximum dilution must not exceed 1 part Fresenius Propoven 1 % with 4 parts of 5 % *m/v* glucose solution or 0,9 % *m/v* sodium chloride solution (minimum concentration 2 mg Fresenius Propoven 1 %/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. Fresenius Propoven 1 % must not be mixed with other solutions for infusion or injection. However co-administration of a 5 % *m/v* glucose solution, 0,9 % *m/v* sodium chloride solution or 0,18 % *m/v* sodium chloride and 4 % *m/v* glucose solution with Fresenius Propoven 1 % is permitted via a Y-piece connector close to the injection site.

To reduce pain at the injection site, lidocaine may be injected immediately before the use of Fresenius Propoven 1 % or Fresenius Propoven 1 % may be mixed, immediately before use, with preservative-free lidocaine injection (20 parts of Fresenius Propoven 1 % with up to 1 part of lidocaine injection solution) under controlled and validated aseptic conditions. The mixture must be administered within 6 hours of preparation. Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Fresenius Propoven 1 %.

Duration of administration:

The duration of administration must not exceed 72 hours.

SIDE EFFECTS

Commonly observed side effects of Fresenius Propoven 1 % are hypotension and respiratory depression. These effects depend on the Fresenius Propoven 1 % dose administered but also on the type of premedication and other concomitant medication. Specifically, the following side effects have been observed:

Immune system disorders:

Rare (< 1:1 000, ≥ 1:10 000)

Clinical features of anaphylaxis, which may include angioneurotic oedema, bronchospasm, erythema and hypotension.

Psychiatric disorders

Rare (< 1:1 000, ≥ 1:10 000)

Euphoria and sexual disinhibition during the recovery period.

Nervous system disorders

Common (< 1:10, ≥ 1:100)

During induction of anaesthesia spontaneous movements and myoclonus, minimal excitation.

Rare (< 1:1 000, ≥ 1:10 000)

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

Very rare (< 1:10 000)

Delayed epileptiform attacks, the delay period ranging from a few hours to several days.

Risk of convulsions in epileptic patients after administration of Fresenius Propoven 1 %.

Cases of postoperative unconsciousness.

Cardiac disorders

Common (< 1:10, ≥ 1:100)

During induction of anaesthesia, bradycardia, tachycardia.

Uncommon (< 1:100, ≥ 1:1 000)

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.

Rare (< 1:1 000, ≥ 1:10 000)

Dysrhythmia during the recovery period.

Vascular disorders

Common (< 1:10, ≥ 1:100)

Hypotension, hot flushes

Uncommon (< 1:100, ≥ 1:1 000)

Marked hypotension. This may require a lowering of the administration rate of Fresenius Propoven 1 % 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

Rare (< 1:1 000, ≥ 1:10 000)

Thrombosis and phlebitis.

Respiratory, thoracic and mediastinal disorders

Common (< 1:10, ≥ 1:100)

During induction of anaesthesia hyperventilation, transient apnoea, coughing, singultus (hiccups).

Uncommon (< 1:100, ≥ 1:1 000)

Coughing during maintenance of anaesthesia

Rare (< 1:1 000, ≥ 1:10 000)

Coughing during the recovery period

Very rare (< 1:10 000)

Pulmonary oedema

Gastrointestinal disorders

Rare (< 1:1 000, ≥ 1:10 000)

Nausea or vomiting during the recovery period.

Very rare (< 1:10 000)

Pancreatitis has been reported after administration of Fresenius Propoven 1 %. A causal relationship, however, could not be established.

Skin and subcutaneous tissue disorders

Very rare (< 1:10 000)

Severe tissue responses after accidental paravenous application.

Renal and urinary disorders

Rare (< 1:1 000, ≥ 1:10 000)

Cases of discolouration of urine following prolonged administration of Fresenius Propoven 1 %.

General disorders and administration site conditions

Very common (> 1:10)

Local pain occurring during the initial injection. Prophylaxis or treatment:

The local pain which may occur during the initial injection of Fresenius Propoven 1 % can be minimized by the co-administration of lidocaine 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 (< 1:1 000, ≥ 1: 10 000): giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

Rare (< 1:1 000, ≥ 1:10 000)

Cases of postoperative fever.

Very rare (< 1:10 000)

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 body weight/h.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

White homogeneous emulsion. Do not use if two layers can be seen after shaking the emulsion.

PRESENTATIONS

5 and 20 clear, colourless glass ampoules with 20 ml emulsion for injection or infusion

5 clear, colourless glass vials with 20 ml emulsion for injection or infusion, sealed with a grey rubber stopper

1, 10 and 15 clear, colourless glass infusion bottles with 50 ml emulsion for injection or infusion, sealed with a grey rubber stopper

1, 10 and 15 clear, colourless glass infusion bottles with 100 ml emulsion for injection or infusion, sealed with a grey rubber stopper

The ampoules/vials/infusion bottles are packed in an outer cardboard carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not refrigerate or freeze.

Protect from light. Do not remove from outer container until required for use.

Single dose vial. Unused portions must be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Fresenius Propoven 1 % (20 ml): 41/2.1/1121

Fresenius Propoven 1 % (50 ml): 41/2.1/1122

Fresenius Propoven 1% (100 ml): 41/2.1/1123

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited
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DATE OF PUBLICATION OF THE PACKAGE INSERT

01 March 2013

1.6.3 Package insert, Fresenius Propoven 1 %

Prescription only medicines(POM)
Botswana: 20 ml BOT1602887 S2
50 ml BOT1602887A S2
100 ml BOT16082887B S2
Uganda: 10091/01/17, POM
Zimbabwe: 2017/1.1/5495, PP