Directions for Use

598/12260725/0721

B. Braun Melsungen AG · 34209 Melsungen, Germany

Propofol-®Lipuro 1%

(10 mg/ml)

Composition
1 ml of emulsion contain

Active substance:
Propofol 10 mg

Excipients:
Soya-bean oil, medium-chain triglycerides, glycerol, Egg phospholipids for injection, sodium oleate, water for injections.

Pharmaceutical form
Emulsion for injection or infusion. In glass ampoules, contents: 20 ml or in glass bottles, contents: 50 ml or 100 ml

Pharmaco-therapeutic group
General anaesthetic

Indications
Propofol-®Lipuro 1 % (10 mg/ml) is a short-acting intravenous general anaesthetic for
- induction and maintenance of general anaesthesia in adults and for use in children above 3 years of age;
- sedation of ventilated adult patients (above 16 years of age) in the intensive care unit; and
- sedation of adult patients (above 16 years of age) for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia.

Contraindications
Propofol-®Lipuro 1 % (10 mg/ml) must not be used
- in patients with known hypersensitivity to propofol or to any of the constituents of the emulsion, see also section "Special warnings and precautions for use" below,
- in children younger than 3 years for induction and maintenance of anaesthesia,
- in patients of 16 years of age or younger for sedation in intensive care.
- in high doses during pregnancy, and obstetric anaesthesia with the exception of termination of pregnancy.

Special warnings and precautions for use
Caution should be exercised in patients with cardiac, respiratory, kidney or liver disease or in hypovolemic, debilitated or epileptic patients in whom Propofol-®Lipuro 1 % (10 mg/ml) should be administered with a reduced administration rate (see dosage). If possible, hypovolemia, cardiac insufficiency, circulatory depression or impaired respiratory function should be compensated before the administration of Propofol-®Lipuro 1% (10 mg/ml).

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-Lipuro should be administered with caution when used to sedate patients undergoing some procedures where spontaneous movements are particularly undesirable, such as ophthalmic surgery.

Use of propofol is not recommended with electroconvulsive therapy.

In patients with severe cardiac impairment it is recommended that Propofol-®Lipuro 1 % (10 mg/ml) is given with great caution and under intensive monitoring.

The risk of relative vagotonia may be increased because propofol lacks vagolytic activity. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia should be considered, especially in situations where the vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause a bradycardia.

The safety and efficacy of Propofol-®Lipuro 1 % (10 mg/ml) for (background) sedation in children younger than 16 years of age have not been demonstrated.

Propofol is not advised for general anaesthesia in children younger than 3 years.

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

Use of propofol for ICU sedation has been associated with a constellation of metabolic disturbances and system organ failures that may result in death.

Reports have been received of combinations of the following: metabolic acidosis, hyperlipidemia, rhabdomyolysis, hepatomegaly, renal failure, Cardiac arrhythmia, Brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the **Propofol infusion syndrome**.

These effects were most frequently 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 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/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the ICU. The patients affected were mainly (but not only) seriously head-injured patients with raised 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/kg/h.

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue propofol when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Attention should be paid to disorders of fat metabolism or to diseases requiring particularly restrictive use of lipid emulsions.

If patients receive parenteral nutrition it is necessary to take account of the amount of lipid infusion as part of the Propofol-®Lipuro 1 % (10 mg/ml) formulation: 1.0 ml of Propofol-®Lipuro1 % (10 mg/ml) contains 0.1 g of fat.

Lipids should be monitored in ICU treatment after 3 days.

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

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

Dilutions with lidocaine solution must not be used in patients with hereditary acute porphyria. Propofol-®Lipuro 1 % (10 mg/ml) contains soya-bean oil, which may rarely cause severe allergic reactions.

In isolated cases there may be phases of postoperative unconsciousness that may be accompanied by an increased muscle tone. The occurrence of such an event is not related to whether the patient was awake or not. Although consciousness returns spontaneously, unconscious patients should be kept under close observation.

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

For use in breastfeeding women, see section Pregnancy and lactation below.

Effects on ability to drive and use machines
After administration of Propofol-®Lipuro 1 % (10 mg/ml) an adequate period of supervision of the awakened patient is indicated to ensure satisfactory recovery. The patient should be advised not to drive, operate machinery or work in potentially dangerous situations.

Patients must be accompanied when going home after discharge and must be instructed to avoid drinking alcohol.

Propofol-®Lipuro 1 % (10 mg/ml) contains no antimicrobial preservatives and supports growth of microorganisms. Asepsis must be maintained for both Propofol-®Lipuro 1 % (10 mg/ml) and the infusion equipment throughout the infusion period. The contents of one ampoule or one bottle of Propofol-®Lipuro 1 % (10 mg/ml) and any syringe containing Propofol-®Lipuro 1 % (10 mg/ml) are for single use in one patient. Do not use if contamination is suspected. Any portion of the contents remaining after use must be discarded.

Pregnancy and lactation
Propofol crosses the placenta and may be associated with neonatal depression. It should therefore not be used in pregnancy or for obstetric anaesthesia, with exception of termination of pregnancy.

Published animal studies of some anaesthetic / sedation drugs have reported adverse effects on brain development in early life and late pregnancy. These studies have demonstrated that anaesthetic / sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and / or potentiate gamma-aminobutyric acid (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. The clinical significance of these non-clinical findings is yet to be determined. However, based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

Propofol enters breast milk only in small amounts. Women should therefore not breastfeed for 24 hours after administration of propofol. Milk produced during this period should be discarded.

Interactions
Propofol-®Lipuro 1 % (10 mg/ml) can be used in combination with other drugs for anaesthesia (pre-medications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics).

Until now no severe interactions with these drugs have been reported. Some of these centrally acting drugs may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Propofol-®Lipuro 1 % (10 mg/ml). Concomitant use of benzodiazepines, parasympatholytic agents or inhalation anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

After additional premedication with opioids there may be a higher incidence and longer duration of apnoea.

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

It should be taken into consideration that concomitant use of propofol and drugs for premedication, inhalation agents, or analgesic agents may potentiate anaesthesia and cardiovascular side effects. Concomitant use of central nervous depressants e.g. alcohol, general anaesthetics, narcotic analgesics will result in intensification of their sedative effects.

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

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

When used in addition to regional anaesthesia the dosage of Propofol-®Lipuro 1 % (10 mg/ml) may need to be reduced.

With the exception of 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, and lidocaine injection 1 %, Propofol-®Lipuro 1 % (10 mg/ml) must not be mixed with other solutions for injection or infusion (refer to "Method of administration", section "Infusion of diluted Propofol-®Lipuro 1 % (10 mg/ml)").

Dosage
General instructions
Propofol-®Lipuro 1 % (10 mg/ml) must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care. Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse-oxymeter) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should always be

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immediately available. For sedationduring surgical or diagnostic procedures Propofol-®Lipuro 1 % (10 mg/ml) should not be given by the same person that carries out the surgical or diagnostic procedure.

Supplementary analgesic drugs are generally required in addition to Propofol-®Lipuro 1 % (10 mg/ml).

Propofol-®Lipuro 1 % (10 mg/ml) is given intravenously. The dosage is adjusted individually according to the patient's response.

General anaesthesia in adults

Induction of anaesthesia

For induction of anaesthesia Propofol-®Lipuro 1 % (10 mg/ml) should be titrated (20 – 40 mg propofol every 10 seconds) against the patient's response until the clinical signs show the onset of anaesthesia. Most adult patients younger than 55 years are likely to require 1.5 to 2.5 mg of propofol/ kg BW (body weight). In older patients and in patients of ASA grades III and IV, especially those with impaired cardiac function, the dosage requirements will be less and the total dose of Propofol-®Lipuro 1 % (10 mg/ml) may be reduced to a minimum of 1 mg of propofol/ kg BW. In these patients lower rates of administration should be applied (approximately 2 ml, corresponding to 20 mg, every 10 seconds).

Maintenance of anaesthesia

Anaesthesia can be maintained by administering Propofol-®Lipuro 1 % (10 mg/ml) either by continuous infusion or by repeat bolus injections. If a technique involving repeat bolus injections is used, increments of 25 – 50 mg of propofol (2.5 – 5.0 ml Propofol-®Lipuro 1 % (10 mg/ml)) may be given according to clinical requirements. For maintenance of anaesthesia by continuous infusion the dosage requirements usually are in the range of 6 – 12 mg/kg BW/h.

In the elderly, in patients of poor general condition, in patients of ASA grade III and IV and in hypovolaemic patients the dosage may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

General anaesthesia in children over 3 years

Induction of anaesthesia:

For induction of anaesthesia Propofol-®Lipuro 1 % (10 mg/ml) should be titrated slowly against the response of the patient until the clinical signs show the onset of anaesthesia. The dosage should be adjusted according to age and/or body weight.

Most patients over 8 years are likely to require approximately 2.5 mg of propofol/kg BW for induction of anaesthesia.

Below this age the dose requirement may be higher (2.5 – 4 mg/kg). Due to the lack of clinical experience, lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Maintenance of general anaesthesia:

For maintenance of general anaesthesia, a satisfactory level of anaesthesia is usually achieved by continuous infusion with a dosage regimen in the range of 9 – 15 mg of propofol/kg BW/h.

Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia (see also section "General instructions" above).

Propofol-®Lipuro 1 % (10 mg/ml) must not be used for induction and maintenance of anaesthesia in children younger than 3 years.

Sedation of adults during intensive care

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol-®Lipuro 1 % (10 mg/ml) be given by continuous infusion. The infusion rate should be adjusted according to the required depth of sedation. Usually satisfactory sedation is achieved with administration rates in the range of 0.3 – 4.0 mg of propofol/kg BW/h. (See also section "Special warnings and precautions for use").

Propofol-®Lipuro 1 % (10 mg/ml) must not be used for sedation in children younger than 16 years.

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 of propofol/kg BW over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol-®Lipuro 1 % (10 mg/ml) infusion to the desired level of sedation.

Most patients will require 1.5 – 4.5 mg of propofol/kg BW/h. The infusion may be supplemented by bolus administration of 10 – 20 mg of propofol (1 – 2 ml Propofol-®Lipuro 1 % (10 mg/ml)) if a rapid increase of the depth of sedation is required. In patients older than 55 years and in patients of ASA grade III and IV lower doses of Propofol-®Lipuro 1 % (10 mg/ml) may be required and the rate of administration may need to be reduced.

Propofol-®Lipuro 1 % (10 mg/ml) must not be used for sedation for diagnostic and surgical procedures in patients of 16 years or younger.

Method of administration

Propofol-®Lipuro 1 % (10 mg/ml) is administered intravenously by injection or continuous infusion either undiluted or diluted with 5 % w/v glucose solution or 0.9 % w/v sodium chloride solution as well as in a 0.18 % w/v sodium chloride and 4 % w/v glucose solution in PVC infusion bags or glass infusion bottles.

Containers should be shaken before use.

Before use the neck of the ampoule or the surface of the rubber stopper of the bottle should be cleaned with medicinal alcohol (spray or swabs). After use tapped containers must be discarded.

Propofol-®Lipuro 1 % (10 mg/ml) contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol-®Lipuro 1 % (10 mg/ml) is to be drawn up aseptically into a sterile syringe or an infusion set immediately after opening the ampoule or breaking the bottle seal. Administration must commence without delay. Asepsis must be maintained for both Propofol-®Lipuro 1 % (10 mg/ml) and the infusion equipment throughout the infusion period.

Any drugs or fluids added to a running Propofol-®Lipuro 1 % (10 mg/ml) infusion must be administered close to the cannula site.

Propofol-®Lipuro 1 % (10 mg/ml) must not be administered via infusion sets with microbiological filters.

The contents of one ampoule or one bottle of Propofol-®Lipuro 1 % (10 mg/ml) and any syringe containing Propofol-®Lipuro 1 % (10 mg/ml) are for single use in one patient. Any portion of the contents remaining after use must be discarded.

Infusion of undiluted Propofol-®Lipuro 1 % (10 mg/ml)

When administering Propofol-®Lipuro 1 % (10 mg/ml) by continuous infusion, it is recommended that burettes, drop counters, syringe pumps or volumetric infusion pumps, should always be used to control the infusion rates. As established for the parenteral administration of all kinds of fat emulsions, the duration of continuous infusion of Propofol-®Lipuro 1 % (10 mg/ml) from one infusion system must not exceed 12 hours. The infusion line and the reservoir of Propofol-®Lipuro 1 % (10 mg/ml) must be discarded and replaced after 12 hours at the latest. Any portion of Propofol-®Lipuro 1 % (10 mg/ml) remaining after the end of infusion or after replacement of the infusion system must be discarded.

Infusion of diluted Propofol-®Lipuro 1 % (10 mg/ml)

For administering infusion of diluted Propofol-®Lipuro 1% (10 mg/ml), burettes, drop counters, syringe pumps, or volumetric infusion pumps should always be used to control infusion rates and to avoid the risk of accidentally uncontrolled infusion of large volumes of diluted Propofol-®Lipuro 1 % (10 mg/ml).

The maximum dilution must not exceed 1 part of Propofol-®Lipuro 1 % (10 mg/ml) with 4 parts of 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 (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically immediately prior to administration and must be used within 6 hours of preparation.

Propofol-®Lipuro 1 % (10 mg/ml) must not be mixed with other solutions for injection or infusion.

Co-administration of Propofol-®Lipuro 1 % (10 mg/ml) together with 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 via a Y-connector close to the injection site is possible.

In order to reduce pain on initial injection, Propofol-®Lipuro 1 % (10 mg/ml) may be mixed with preservative-free lidocaine injection 1 % (mix 20 parts of Propofol-®Lipuro 1 % (10 mg/ml) with up to 1 part of lidocaine injection 1 %).

Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-®Lipuro 1 % (10 mg/ml) through the same intravenous line, it is recommended that the line be rinsed prior to administration.

Duration of use

Propofol-®Lipuro 1 % (10 mg/ml) can be administered for a maximum period of 7 days.

Overdose

Accidental overdose is likely to cause cardio-respiratory depression.

Treat respiratory depression by artificial ventilation. Cardiovascular depression may require lowering the patient's head and administering plasma expanders and pressor agents.

Undesirable effects

During induction of anaesthesia; hypotension and transient apnoea may occur depending on the dose of propofol, the type of premedication and other concomitant medication. Occasionally occurring marked hypotension may require the use of intravenous fluids, if necessary vasoconstrictive drugs, and slower administration of Propofol-®Lipuro 1 % (10 mg/ml). 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 hypovolemia.

During general anaesthesia bradycardia occurred, occasionally with progressive severity (asystole). The intravenous administration of an anticholinergic drug prior to induction or during maintenance of anaesthesia should be considered (see also "Special warnings and special precautions for use").

During induction of anaesthesia spontaneous movements and myocloni are likely to be observed.

During maintenance of anaesthesia coughing occasionally occurs.

During the recovery period, nausea, vomiting, headache, shivering and sensations of cold have seldom been reported as well as euphoria and sexual disinhibition.

Rarely, epileptiform convulsions including opisthotonus may occur, in isolated cases delayed by hours or days after termination of administration of propofol. In isolated cases, after administration to epileptic patients, convulsions have been observed.

There have been reports of rare cases of post-operative fever and discoloration of urine following prolonged administration of Propofol-®Lipuro 1 % (10 mg/ml) as well as severe cases of hypersensitivity reactions (anaphylaxis), which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Pulmonary edema, hypotension, asystole, bradycardia and convulsions have been reported.

In very rare cases rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, sometimes with fatal outcome, have been observed when propofol was administered at dosages in excess of 4 mg of propofol/kg BW/h for sedation in the ICU (see also "Special warnings and precautions for use").

The local pain that may occur during the initial injection of Propofol-®Lipuro 1 % (10 mg/ml) can be minimized by the coadministration of lidocaine (see "Method of administration", section „Infusion of diluted Propofol-®Lipuro 1 % (10 mg/ml)") and by injection/infusion into the larger veins of the forearm and antecubital fossa.

Thrombosis and phlebitis are rare.

After co-administration of lidocaine the following undesirable effects may occur: giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

There are isolated reports of severe tissue reactions after accidental extravascular administration.

Note

Patients are advised to inform their doctor or pharmacist if they experience any adverse reaction not described in this leaflet.

Expiry date

The product must not be used beyond the expiry date stated on the labelling.

Instructions for storage / use / handling

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

Containers should be shaken before use.

Discard any unused portions at the end of the administration.

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

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