Directions for Use
B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Germany.

Propofol-Lipuro 1% (10 mg/ml)

Emulsion for Injection/Infusion

Composition

Active substance:

1 ml of emulsion contains 10 mg of propofol.
One ampoule or vial of 20 ml contains 200 mg of propofol

Excipients:

Soya-bean oil, refined, 50 mg/ml,
medium-chain triglycerides,
glycerol,
egg lecithin,
sodium oleate, equivalent to 0.03 mg sodium/ml
water for injections.

Pharmaceutical form

Emulsion for injection or infusion

Product description

White milky oil-in-water emulsion

Pharmaco-therapeutic group

Other general anaesthetics, ATC code N01AX10

Pharmacodynamic Properties

Mechanism of action, pharmacodynamic effect

After intravenous injection of Propofol-Lipuro 1% (10 mg/ml), 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 normalises during maintenance of anaesthesia.

The formulation of propofol in a mixed medium- and long-chain triglyceride emulsion leads to lower concentrations of free medicinal product in the aqueous phase compared to pure long-chain triglyceride emulsions. This difference may explain the reduced pain frequency and intensity observed with Propofol-Lipuro formulations in comparative clinical studies, especially with Propofol-Lipuro 5 mg/ml, due to the very low concentration of free propofol.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

Pharmacokinetic Properties

After i.v administration about 98% of propofol is bound to plasma protein. After i.v bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (alpha-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 beta-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue. Clearance is higher in children compared with adults.

The central volume distribution is in the range of 0.2-0.79 l/kg BW, the steady-state volume of distribution in the range of 1.8-5.3 l/kg BW. Propofol is rapidly cleared from the body (total clearance approx. 2 l/min). Clearance occurs by metabolism, 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% is excreted unchanged in the urine.

Indications

Propofol-Lipuro 1% (10 mg/ml) is a short-acting intravenous general anaesthetic for:-

- Induction and maintenance of general anaesthesia
- Sedation of ventilated patients in the intensive care unit
- Sedation 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 one of the excepients
- in children younger than 3 years for induction and maintenance of anaesthesia
- in children younger than 16 years of age for sedation
- in high dose during pregnancy, and obstetric anaesthesia with the exception of termination of pregnancy.

Special warnings and precautions for use

Propofol should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care).

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 should not be administered by the person conducting the diagnostic or surgical procedure.

The abuse of propofol, predominantly by health care professionals, has been reported. As with other general anaesthetics, the administration of propofol without airway care may result in fatal respiratory complications.

When propofol 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.

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.

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of propofol. Very rarely the use of propofol may be associated with the development of a period of post-operative 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, 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 agents that may sedate (e.g. benzodiazepines, opiates, alcohol.)

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 (see "**Dosage**").

Propofol clearance is blood flow dependent, therefore, concomitant medication which reduces cardiac output will also reduce propofol clearance.

When propofol is administered to an epileptic patient, there may be a risk of convulsion.

Propofol lacks vagolytic activity and 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 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 bradycardia.

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

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol 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-Lipuro 1% (10 mg/ml) contains 0.1 g of fat.

The use of Propofol-Lipuro 1% (10 mg/ml) is not recommended 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.

Advisory statements concerning Intensive Care Unit management

The safety and efficacy of propofol for (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in intensive care units (ICU).

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

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 pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol (usually following extended dosing at dose rates greater than 4 mg/kg/h).

Prescribers should be alert to these events and consider decreasing the propofol dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. All sedative and therapeutic agents used in the intensive care unit (ICU), including propofol, should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.

Additional precautions

Propofol-Lipuro 1% (10 mg/ml) contains no antimicrobial preservatives and supports growth of micro-organisms.

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

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

This medicinal product contains less than 1 mmol (23 mg) sodium in 100 ml, i.e. essentially 'sodium free'.

Interactions

Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of propofol may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.

Incompatibilities

Propofol-Lipuro 1% (10 mg/ml) must not be mixed with other medicinal products except those mentioned in sections **"Dosage,** *Method of administration"* and **"Instructions for storage / use / handling".**

Pregnancy and lactation

Pregnancy

The safety of propofol during pregnancy has not been established. Propofol should not be given to pregnant woman except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Propofol can, however, be used during an induced abortion.

Breast-feeding

Studies of breast-feeding mothers showed that small quantities of propofol are excreted in human milk. Women should therefore not breast-feed for 24 hours after administration of propofol. Milk produced during this period should be discarded.

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 use of propofol.

Propofol induced impairment is not generally detectable beyond 12 hours (please see **"Special warnings and precautions for use").**

Dosage

General instructions

Propofol-Lipuro 1% (10 mg/ml) must only to 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 patient airways, artificial ventilation, and other resuscitation facilities should always be immediately available. For sedation during 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

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

Maintenance

Anaesthesia can be maintained by administrating Propofol 1% (10 mg/ml) by continuous infusion or by repeat bolus injections. If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml Propofol-Lipuro 1% (10 mg/ml)) to 50 mg (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 to a minimum of 4 mg/ kg BW/h.

598/12611389/0817

Direction for Use

Propofol-Lipuro 1% (10 mg/ml)

Emulsion for Injection/Infusion

B. Braun Melsungen AG
Carl-Braun-Straße 1,
34212 Melsungen,
Germany

schwarz

Dokument = 210 x 596 mm
2 Seiten

Lätus

2700

MY___598

598/12611389/0817
Propofol-Lipuro 1% (10 mg/ml)
L05
GIF (GA)
Standort Berlin

Font size: 9,5 pt.

G 151030

General anaesthesia in children over 3 years

Induction

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 2.5mg/kg BW of Propofol-Lipuro 1% (10 mg/ml) 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 anaethesia, a satisfactory level of anaethesia is usually achieved by continuous infusion with a dosage regimen in the range of 9-15 mg/ 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 anaethesia 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/kg BW/h.

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

Sedation of 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/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/kg BW/h. The infusion may be supplemented by bolus administration of 10–20 mg (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 children younger than 16 years.

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.

<u>Infusion of undiluted Propofol-Lipuro 1 % (10 mg/ml)</u>

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 after12 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.

<u>Infusion of diluted Propofol-Lipuro 1 % (10 mg/ml)</u>

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.

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

Undesirable effects

Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, 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.

Table of Adverse Drug Reactions

System Organ Class	Frequency	Undesirable Effects
Immune system disorders:	Very rare (<1/10 000)	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, drug abuse [8]
Nervous system disorders:	Common (>1/100, <1/10)	Headache during recovery phase
	Rare (>1/10 000, <1/1000)	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare (<1/10 000)	Postoperative unconsciousness
	Frequency not known [9]	Involuntary movements
Cardiac disorders:	Common (>1/100, <1/10)	Bradycardia [1]
	Very rare (<1/10 000)	Pulmonary oedema
	Frequency not known [9]	Cardiac arrhythmia [5], cardiac failure [5], [7]
Vascular disorders:	Common (>1/100, <1/10)	Hypotension [2]
	Uncommon (>1/1000, <1/100)	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders:	Common (>1/100, <1/10)	Transient apnoea during induction
Gastrointestinal disorders:	Common (>1/100, <1/10)	Nausea and vomiting during recovery phase
	Very rare (<1/10 000)	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	Very rare (<1/10 000)	Discolouration of urine following prolonged administration
	Frequency not known [9]	Renal failure [5]
Reproductive system and breast	Very rare (<1/10 000)	Sexual disinhibition
General disorders and administration site conditions:	Very common (>1/10)	Local pain on induction [4]
Investigations	Frequency not known [9]	Brugada type ECG [5], [6]
Injury, poisoning and procedural complications:	Very rare (<1/10 000)	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] Very rare reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
[4] May be minimised by using the larger veins of the forearm and antecubital fossa. With Propofol-Lipuro 1% (10 mg/ml) local pain can also be minimised by the co-administration of lidocaine.
[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 **"Special warnings and precautions for use".**
[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] Drug abuse, predominantly by health care professionals.
[9] Not known as it cannot be estimated from the available clinical trial data.

<u>Note</u>

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.

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Containers should be shaken before use. If two layers can be seen after shaking the product should not be used.

Propofol-Lipuro 1% (10 mg/ml) should only be mixed with the following products: 5 % w/v glucose solution, 0.9 % w/v sodium chloride solution, or 0.18 % sodium chloride and 4 % w/v glucose solution, and preservative-free lidocaine injection 1 % (see section "**Dosage** / *Method of administration* / Infusion of diluted Propofol-Lipuro 1% (10 mg/ml)")

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.

Pack sizes

Glass ampoules: 20 ml

Date of last revision: 04.2016

Product Registration Holder:
B. Braun Medical Industries Sdn.Bhd.
11900 Bayan Lepas, Penang, Malaysia.

Manufactured by:
B. Braun Melsungen AG
Carl-Braun-Straße 1,
34212 Melsungen,
Germany