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Directions for Use

B. Braun Melsungen AG · 34209 Melsungen, Germany

Propofol-®Lipuro 2 % (20 mg/ml)

Composition

1 ml of emulsion contains 20 mg of propofol.

Active substance:

Propofol

Excipients:

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

Pharmaceutical form

Emulsion for injection or infusion

Pharmaco-therapeutic group

General anaesthetic

Indications

Propofol-Lipuro 2 % (20 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
- 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 2 % (20 mg/ml) must not be used:

- in patients with known hypersensitivity to propofol or to any of the constituents of the emulsion,
- in patients who are allergic to soya or peanut,
- 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 hypovolaemic, debilitated or epileptic patients in whom Propofol-Lipuro 2 % (20 mg/ml) should be administered with a reduced administration rate (see **"Dosage"**). If possible, hypovolaemia, cardiac insufficiency, circulatory depression or impaired respiratory function should be compensated before the administration of Propofol-Lipuro 2 % (20 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 2 % (20 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.

Propofol is contraindicated for general anaesthesia in children younger than 3 years of age.

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. The safety and efficacy of Propofol-Lipuro 2 % (20 mg/ml) for (background) sedation in children younger than 16 years of age have not been demonstrated.

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 of propofol/kg body weight (BW)/h.

This exceeds the maximum dosage of 4 mg of propofol/kg BW/h currently advised for sedation in the ICU. The patients affected were mainly (but not only) seriously head-injured patients with raised 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 of propofol/kg BW/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 2 % (20 mg/ml) formulation: 1.0 ml of Propofol-Lipuro 2 % (20 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.

In order to reduce pain on initial injection of Propofol-Lipuro 2 % (20 mg/ml) for induction of general anaesthesia, lidocaine may be injected immediately prior to the administration of Propofol-Lipuro 2 % (20 mg/ml). Care must be taken not to administer lidocaine to patients with hereditary acute porphyria

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 2 % (20 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.

Pregnancy and lactation

The safety of propofol during pregnancy has not been established. Therefore, propofol should not be used in pregnant woman unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression.

High doses (more than 2.5 mg of propofol/kg BW for induction or 6 mg of propofol/kg BW/h for maintenance of anaesthesia) should 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 2 % (20 mg/ml) can be used in combination with other medicinal products for anaesthesia (premedications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics). Until now no 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-Lipuro 2 % (20 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 medicinal products 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 2 % (20 mg/ml) may need to be reduced.

Propofol-Lipuro 2 % (20 mg/ml) must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol-Lipuro 2 % (20 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.

Dosage

General instructions

Propofol-Lipuro 2 % (20 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 immediately available. For sedation during surgical or diagnostic procedures Propofol-Lipuro 2 % (20 mg/ml) should not be given by the same person that carries out the surgical or diagnostic procedure.

Supplementary analgesic medicinal products are generally required in addition to Propofol-Lipuro 2 % (20 mg/ml).

Propofol-Lipuro 2 % (20 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 2 % (20 mg/ml) should be titrated (20 – 40 mg of 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.

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 2 % (20 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 1 ml, corresponding to 20 mg, every 10 seconds).

Maintenance of anaesthesia

Anaesthesia is maintained by administering Propofol-Lipuro 2 % (20 mg/ml) by continuous infusion. The dosage requirements usually are in the range of 4 – 12 mg of propofol/kg BW/h.

In the elderly, in patients of poor general condition, in patients of ASA grades 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 of age

Induction of anaesthesia

For induction of anaesthesia Propofol-Lipuro 2 % (20 mg/ml) should be titrated slowly against the patient's response until the clinical signs show the onset of anaesthesia. The dosage should be adjusted according to age and/ or BW.

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 of propofol/kg BW).

Due to the lack of clinical experience, lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Propofol-Lipuro 2 % (20 mg/ml) is contraindicated for induction of anaesthesia in children below 3 years of age.

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 *"General instructions"* above).

Propofol-Lipuro 2 % (20 mg/ml) is contraindicated for maintenance of anaesthesia in children below 3 years of age.

Sedation of ventilated patients in the intensive care unit

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol-Lipuro 2 % (20 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 **"Special warnings and precautions for use"**).

Propofol is not indicated for sedation in the intensive care unit of patients of 16 years of age or younger (see **"Contraindications"**).

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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 2 % (20 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 (0.5 – 1 ml Propofol-Lipuro 2 % (20 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 2 % (20 mg/ml) may be required and the rate of administration may need to be reduced.
Propofol-Lipuro 2 % (20 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 2 % (20 mg/ml) is administered undiluted intravenously. Containers should be shaken before use.
Before use, 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 2 % (20 mg/ml) contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol-Lipuro 2 % (20 mg/ ml) is to be drawn up aseptically into a sterile syringe or an infusion set immediately after breaking the bottle seal. Administration must commence without delay. Asepsis must be maintained for both Propofol-Lipuro 2 % (20 mg/ml) and the infusion equipment throughout the infusion period.
Any medicinal products or fluids added to a running Propofol-Lipuro 2 % (20 mg/ml) infusion must be administered close to the cannula site. Propofol-Lipuro 2 % (20 mg/ml) must not be administered via infusion sets with microbiological filters.
The contents of one bottle of Propofol-Lipuro 2 % (20 mg/ml) and any syringe containing Propofol-Lipuro 2 % (20 mg/ml) are for **single use** in **one** patient.
Any portion of the contents remaining after use must be discarded.
For administration of Propofol-Lipuro 2 % (20 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 2 % (20 mg/ml) from **one** infusion system must not exceed 12 hours. The infusion line and the reservoir of Propofol-Lipuro 2 % (20 mg/ml) must be discarded and replaced after 12 hours at the latest. Any portion of Propofol-Lipuro 2 % (20 mg/ml) remaining after the end of infusion or after replacement of the infusion system must be discarded.
Propofol-Lipuro 2 % (20 mg/ml) must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol-Lipuro 2 % (20 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 of Propofol-Lipuro 2 % (20 mg/ml) for induction of general anaesthesia, lidocaine may be injected immediately prior to the injection of Propofol-Lipuro 2 % (20 mg/ml) (see **"Special warnings and precautions for use"**).
Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-Lipuro 2 % (20 mg/ml) through the same intravenous line, the line should be rinsed prior to administration.

Duration of use
Propofol-Lipuro 2 % (20 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
The most commonly observed undesirable 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. Specifically, the following side effects have been observed:

Immune system disorders
Rare (≥ 1:10 000 to < 1:1000):
Severe hypersensitivity reactions (anaphylaxis), which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Psychiatric disorders
Rare (≥ 1:10 000 to < 1:1000): Euphoria and sexual disinhibition during the recovery period.

Nervous system disorders
Common (≥ 1:100 to < 1:10):
During induction of anaesthesia spontaneous movements and myocloni are likely to be observed.

Uncommon (≥ 1:1000 to < 1:100)
Dystonia and other involuntary movement disorders.

Rare (≥ 1:10 000 to < 1: 1000):
Headache, vertigo, shivering and sensations of cold during the recovery period; Epileptiform convulsions including opisthotonus.

Very rare (< 1:10 000), not known (cannot be estimated from the available data):
Delayed epileptiform attacks, the delay period ranging from a few hours to several days.
Convulsions have been observed in epileptic patients after administration of propofol (isolated cases).
Cases of postoperative unconsciousness, cf. **"Special warnings and precautions for use"**.

Cardiac and circulatory disorders

Common (≥ 1:100 to < 1:10): Mild or moderate hypotension

Uncommon (≥ 1:1000 to < 1:100):
Marked hypotension. This may require the use of intravenous fluids, if necessary vasoconstrictive medicinal products, and slower administration of Propofol-Lipuro 2 % (20 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.

Rare (≥ 1:10 000 to < 1:1000):
Cardiac arrhythmia during the recovery period;
Bradycardia during general anaesthesia, in some cases with progressive severity (up to asystole). The intravenous administration of an anticholinergic medicinal products prior to induction or during maintenance of anaesthesia should be considered (see also **"Special warnings and precautions for use"**).

Respiratory, thoracic and mediastinal disorders
Common(≥ 1:100 to < 1:10):
During induction of anaesthesia hyperventilation, transient apnoea, coughing

Uncommon (≥ 1:1000 to < 1:100): Coughing during maintenance of anaesthesia.

Rare (≥ 1:10 000 to < 1:1000): Coughing during the recovery period.

Very rare (< 1:10 000), not known (cannot be estimated from the available data): Pulmonary oedema after administration of propofol (isolated cases)

Gastrointestinal disorders
Common (≥ 1:100 to < 1:10): Singultus during induction of anaesthesia

Rare (≥ 1:10 000 to < 1:1000): Nausea or vomiting during the recovery period.

Very rare (< 1:10 000), not known (cannot be estimated from the available data):
Pancreatitis occurred after administration of propofol. A causal relationship, however, could not be established.

Renal and urinary disorders
Rare (≥ 1:10 000 to < 1:1000):
Cases of discoloration of urine following prolonged administration of Propofol-Lipuro 2 % (20 mg/ml)

General disorders and administration site conditions
Common (≥ 1:100 to < 1:10): Hot flushes during induction of anaesthesia

Rare (≥ 1:10 000 to < 1:1000): Cases of post-operative fever

Very rare (< 1:10 000), not known (cannot be estimated from the available data):
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. These effects have been observed in patients in intensive care with doses exceeding 4 mg of propofol/kg BW/h. For more details, see **"Special warnings and precautions for use"**.

Very common (> 1:10):
Local pain occurring during the initial injection. Prophylaxis or treatment see below.

Rare (≥ 1:10 000 to < 1:1000): Thrombosis and phlebitis.

Very rare (< 1:10 000), not known (cannot be estimated from the available data):
Severe tissue reactions after accidental extravascular administration (isolated cases).
The local pain that may occur during the initial injection of Propofol-Lipuro 2 % (20 mg/ml) can be minimized by co-administration of lidocaine (see **"Method of administration"**) 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: giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

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.
Keep container in the outer carton.
Containers should be shaken before use.
Any unused product or waste material should be disposed of in accordance with local requirements.
If two layers can be seen after shaking the product should not be used

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