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Directions for Use

B. Braun Melsungen AG, 34209 Melsungen, Germany

Propofol-®Lipuro 2% (20 mg/ml)

Emulsion for Injection/Infusion

Composition

Active substance:

1 ml of emulsion contains 20 mg of propofol.
One vial of 50 ml contains 1000 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 Dosage Form

Emulsion for injection or infusion

Product Description

White milky oil-in-water emulsion

Pharmacodynamic properties

Pharmaco therapeutic group: other general anaesthetics, ATC-code N01AX10.

Mechanism of action, pharmacodynamic effect

After intravenous injection of Propofol-®Lipuro 2% (20 mg/ml), onset of the hypnotic effect is rapid. 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, 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 the lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

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

Distribution

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 is 2 – 4 minutes.

During elimination the decline of blood levels is slower. The elimination half-life during the ß-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the redistribution of propofol from weakly perfused tissue.

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.

Biotransformation

Propofol is mainly metabolized in the liver to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive.

Elimination

Propofol is rapidly cleared from the body (total clearance approx. 2 l/min). Clearance occurs by metabolism, mainly in the liver, where it is blood flow dependent. Clearance is higher in children compared with adults. 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 2% (20 mg/ml) is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia. Propofol-®Lipuro 2% (20 mg/ml) may also be used for sedation of ventilated adult patients receiving intensive care.

Contraindications

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

- in patients with known hypersensitivity to propofol, or to one of the excipients
- in children younger than 3 years for induction and maintenance of anesthesia
- in children younger than 16 years of age for sedation
- in high dose during pregnancy, and obstetric anesthesia with 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 2% (20 mg/ml) contains 0.1 g of fat.

The use of Propofol-®Lipuro 2% (20 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.

Propofol-®Lipuro 2% (20 mg/ml) is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

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 of propofol/kg BW/h.

Warning

Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care.

There have been very rare reports of epileptiform movement in the epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol.

Additional precautions

Propofol-®Lipuro 2% (20 mg/ml) contains no antimicrobial preservatives and supports growth of microorganisms.
When propofol is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after breaking the vial 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 2% (20 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 women 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 breastfeed 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

Supplementary analgesic agents are generally required in addition to Propofol-®Lipuro 2% (20 mg/ml). Propofol-®Lipuro 2% (20 mg/ml) has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalation agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Propofol-®Lipuro 2% (20 mg/ml) may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

A. Adults

INDUCTION OF GENERAL ANAESTHESIA

Propofol-®Lipuro 2% (20 mg/ml) should be used to induce anaesthesia by infusion and only in those patients who will receive Propofol-®Lipuro 2% (20 mg/ml) for maintenance of anaesthesia. Administration of Propofol-®Lipuro 2% (20 mg/ml) by bolus injection is not recommended. In unpremedicated and premedicated patients, it is recommended that Propofol-®Lipuro 2% (20 mg/ml) should be titrated (approximately 40 mg every 10 seconds in an average healthy adult by infusion) against the response of the patient until the 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/kg of Propofol-®Lipuro 2% (20 mg/ml). The total dose required can be reduced by lower rates of administration (20 - 50 mg/min). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg every 10 seconds).

MAINTENANCE OF GENERAL ANAESTHESIA

Anaesthesia can be maintained by administering Propofol-®Lipuro 2% (20 mg/ml) by continuous infusion to maintain the depth of anaesthesia required. Continuous Infusion: The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia. Repeat Bolus Injections: Administration of Propofol-®Lipuro 2% (20 mg/ml) by bolus injection is not recommended.

SEDATION DURING INTENSIVE CARE

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Propofol-®Lipuro 2% (20 mg/ml) be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 to 4.0 mg/kg/h should achieve satisfactory sedation.

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B. Elderly Patients

In elderly patients the dose requirement for induction of anaesthesia with Propofol-®Lipuro 2% (20 mg/ml) is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Where Propofol-®Lipuro 2% (20 mg/ml) is used for maintenance of anaesthesia or sedation the rate of infusion or target concentration should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

C. Children

INDUCTION OF GENERAL ANAESTHESIA

Propofol-®Lipuro 2% (20 mg/ml) is not recommended for use in children less than 3 years of age (see section Possible Adverse Reactions). Administration of Propofol-®Lipuro 2% (20 mg/ml) by bolus injection is not recommended when used to induce anaesthesia in children. It is recommended that Propofol-®Lipuro 2% (20 mg/ml) be given by slow infusion until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of Propofol-®Lipuro 2% (20 mg/ml) for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

MAINTENANCE OF GENERAL ANAESTHESIA

Propofol-®Lipuro 2% (20 mg/ml) is not recommended for use in children less than 3 years of age. Administration of Propofol-®Lipuro 2% (20 mg/ml) by bolus injection is not recommended. Anaesthesia can be maintained by administering Propofol-®Lipuro 2% (20 mg/ml) by infusion to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

SEDATION DURING INTENSIVE CARE

Propofol-®Lipuro 2% (20 mg/ml) is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

D. Administration

Administration of Propofol-®Lipuro 2% (20 mg/ml) by bolus injection is not recommended. Propofol-®Lipuro 2% (20 mg/ml) should not be diluted. Propofol-®Lipuro 2% (20 mg/ml) can be used for infusion undiluted from plastic syringes or glass infusion bottles.

When Propofol-®Lipuro 2% (20 mg/ml) is used undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates. Propofol-®Lipuro 2% (20 mg/ml) may be administered via a Y-piece close to the injection site, into infusions of Dextrose 5% Intravenous Infusion, Sodium Chloride 0.9% Intravenous Infusion or Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion.

Overdose

Accidental overdoseage 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 2% (20 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 section 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.

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.

Packaging Available

Pack size: 10 x 50 ml

Instructions for storage / use / handling

Do not store above 30 °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 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 glucose 50 mg/ml (5 % w/v) solution or sodium chloride 9 mg/ml (0.9 % w/v) solution, or sodium chloride 1.8 mg/ml (0.18 % w/v) and glucose 40 mg/ml (4 % w/v) solution via a Y-connector close to the injection site is possible.

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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

B. Braun Melsungen AG
34209 Melsungen, Germany