

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the Medicinal Product

Propofol-Lipuro 2%

2 Qualitative and Quantitative Composition

Propofol 20 mg/ml

Excipient(s) with known effect:

Soya-bean oil, refined

For a full list of excipients, see section 6.1.

3 Pharmaceutical Form

Emulsion for injection or infusion
White milky oil-in-water emulsion

4 Clinical Particulars

4.1 Therapeutic indications

Propofol-Lipuro 2% is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children > 3 years
- sedation of ventilated patients >16 years of age in the intensive care unit
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children > 3 years.

4.2 Posology and method of administration

General instructions

Propofol-Lipuro 2% 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 be immediately available at all times. For sedation during surgical or diagnostic procedures Propofol-Lipuro 2% 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%

Posology

Propofol-Lipuro 2% 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% 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/kg body weight.

In patients over this age 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% may be reduced to a minimum of 1 mg/kg body weight. 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% by continuous infusion. The dosage requirements usually are in the range of 4 – 12 mg/kg body weight/h.

In elderly patients, in patients of poor general condition, in patients of ASA grades III and IV and in hypovolaemic patients the dosage may have to 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% should be slowly titrated 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 of age require approximately 2.5 mg/kg body weight of propofol for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, the dose requirements may be higher (2.5 – 4 mg/kg body weight)

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering Propofol Lipuro 2% 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 – 15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA III and IV patients lower doses are recommended (see also section 4.4)

- *Sedation of ventilated patients in the intensive care unit*

For sedation during intensive care, it is advised that Propofol-Lipuro 2% should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3 – 4.0 mg of propofol per kg body weight per hour (see section 4.4).

Propofol is not indicated for sedation of patients of 16 years or younger in intensive care (see section 4.3). Administration of propofol by Target Controlled Infusion (TCI) system is not advised for sedation in the intensive care unit.

- *Sedation for diagnostic and surgical procedures in adults*

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 body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol-Lipuro 2% infusion to the desired level of sedation. Most patients will require 1.5 – 4.5 mg/kg body weight/h.

In patients older than 55 years and in patients of ASA grade III and IV lower doses of Propofol-Lipuro 2% may be required and the rate of administration may need to be reduced.

According to required dose, alternatively Propofol 1 % may be used.

- *Sedation for diagnostic and surgical procedures in children over 3 years of age*

Doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1 – 2 mg/kg body weight of propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating of propofol infusion to the desired level of sedation. Most patients require 1.5 – 9 mg/kg/h of propofol.

In ASA III and IV patients lower doses may be required.

Method and duration of administration

- *Method of administration*

Intravenous use

Propofol-Lipuro 2% is administered undiluted intravenously. Containers should be shaken before use.

Before use, the surface of the rubber stopper of the vial 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 vial 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 vial 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% 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.

This medicinal product must not be mixed with other medicinal products, but may be co-administered with those mentioned in section 6.6.

In order to reduce pain on initial injection of Propofol-Lipuro 2% for induction of general anaesthesia, lidocaine may be injected immediately prior to the injection of Propofol-Lipuro 2%.

Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-Lipuro 2% through the same intravenous line, the line should be rinsed prior to administration.

Propofol may also be used by Target Controlled Infusion. Due to the different algorithms available on the market for dosage recommendations please refer to the instructions for use leaflet of the device manufacturer.

- *Duration of administration*

Propofol-Lipuro 2% can be administered for a maximum period of 7 days.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Propofol-Lipuro 2% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

Propofol-Lipuro 2% must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

4.4 Special warnings and precautions for use

Propofol-Lipuro 2% 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 and oxygen enrichment and other resuscitative facilities should be readily available at all times. Propofol-Lipuro 2% should not be administered by the person conducting the diagnostic or surgical procedure.

Abuse of, and dependence on Propofol-Lipuro 2%, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Propofol-Lipuro 2% without airway care may result in fatal respiratory complications.

When Propofol-Lipuro 2% 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.

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other agents.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Propofol-Lipuro 2% during the period of anaesthetic maintenance.

As with other sedative agents, when Propofol-Lipuro 2% 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-Lipuro 2%. Very rarely, the use of Propofol-Lipuro 2% 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-Lipuro 2% induced impairment is not generally detectable beyond 12 hours. The effects of Propofol-Lipuro 2%, 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 (Eg. 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. Propofol-Lipuro 2% clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Propofol-Lipuro 2% clearance.

Propofol-Lipuro 2% 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 vagal tone is likely to predominate or when Propofol-Lipuro 2% is used in conjunction with other agents likely to cause a bradycardia.

When Propofol-Lipuro 2% is administered to an epileptic patient, there may be a risk of convulsion.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously (see section 4.2).

Use is not recommended with electroconvulsive treatment.

As with other anaesthetics sexual disinhibition may occur during recovery.

The benefits and risks of the proposed procedure should be considered prior to proceeding with repeated or prolonged use (>3 hours) of propofol in young children (< 3 years) and in pregnant women as there have been reports of neurotoxicity in preclinical studies, see Section 5.3.

Paediatric population

The use of Propofol is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) 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% is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

Advisory statements concerning Intensive Care Unit management

Use of propofol emulsion infusions for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death. 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. Combinations of these events have been referred to as the Propofol Infusion Syndrome. These events were mostly 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 the intensive care unit.

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-Lipuro 2% (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).

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 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. 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% contains approximately 0.1 g of fat.

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

Additional Precautions

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the 'propofol infusion syndrome' may be similar.

Propofol-Lipuro 2% contains no antimicrobial preservatives and supports growth of micro-organisms.

When Propofol-Lipuro 2% is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both Propofol-Lipuro 2% and infusion equipment throughout the infusion period. Any infusion fluids added to the Propofol-Lipuro 2% line must be administered close to the cannula site. Propofol-Lipuro 2% must not be administered via a microbiological filter.

Propofol-Lipuro 2% and any syringe containing Propofol-Lipuro 2% 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.

4.5 Interaction with other medicinal products and other forms of interaction

Propofol-Lipuro 2% 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-Lipuro 2% may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques. Profound hypotension has been reported following anaesthesia with propofol in patients treated with rifampicin.

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol Propofol-Lipuro 2% (see Section 4.4).

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Teratology studies in rats and rabbits showed no teratogenic effects.

The safety of Propofol-Lipuro 2% during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Propofol-Lipuro 2% should not be given to pregnant women except when absolutely necessary. Propofol-Lipuro 2% can, however, be used during an induced abortion.

Obstetrics

Propofol-Lipuro 2% crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia.

Breast-feeding

Studies of breast-feeding mothers showed that small quantities of Propofol-Lipuro 2% are excreted in human milk. Woman should therefore not breast-feed for 24 hours after administration of Propofol-Lipuro 2%. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and to use machines

Propofol-Lipuro 2% has moderate influence on the 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 general anaesthesia.

Propofol-Lipuro 2% induced impairment is not generally detectable beyond 12 hours (Section 4.4).

4.8 Undesirable effects

General

Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation.

Side effects during induction, maintenance and recovery occur uncommonly.

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-Lipuro 2% may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

The following definitions of frequencies are used:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Table of Adverse Drug Reactions

System Organ Class	Frequency	Undesirable Effects
Immune system disorders	Very rare	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and Nutritional disorder	Not known ⁽⁹⁾	Metabolic acidosis ⁽⁵⁾ , hyperkalaemia ⁽⁵⁾ , hyperlipidaemia ⁽⁵⁾

Psychiatric disorders	Not known ⁽⁹⁾	Euphoric mood. Drug abuse and drug dependence ⁽⁸⁾
Nervous system disorders	Common	Headache during recovery phase
	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare	Postoperative unconsciousness
	Not known ⁽⁹⁾	Involuntary movements
Cardiac disorders	Common	Bradycardia ⁽¹⁾
	Very rare	Pulmonary oedema
	Not known ⁽⁹⁾	Cardiac arrhythmia ⁽⁵⁾ , cardiac failure ^{(5), (7)}
Vascular disorders	Common	Hypotension ⁽²⁾
	Uncommon	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Common	Transient apnoea during induction
	Not known ⁽⁹⁾	Respiratory depression (dose-dependent)
Gastrointestinal disorders	Common	Nausea and vomiting during recovery phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known ⁽⁹⁾	Hepatomegaly ⁽⁵⁾
Musculoskeletal and connective tissue disorders	Not known ⁽⁹⁾	Rhabdomyolysis ^{(3), (5)}
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Not known ⁽⁹⁾	Renal failure ⁽⁵⁾
Reproductive system and breast disorders	Very rare	Sexual disinhibition
	Not known	Priapism
General disorders and administration site conditions	Very common	Local pain on induction ⁽⁴⁾
	Very rare	Tissue necrosis ⁽¹⁰⁾ following accidental extravascular administration

	Not known ⁽⁹⁾	Local pain, swelling following accidental extravascular administration
Investigations	Not known ⁽⁹⁾	Brugada type ECG ^{(5), (6)}
Injury, poisoning and procedural complications	Very rare	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% 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 4.4.
- (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) Abuse of and drug dependence on propofol, predominantly by health care professionals.
- (9) Not known as it cannot be estimated from the available clinical trial data.
- (10) Necrosis has been reported where tissue viability has been impaired.

Dystonia/dyskinesia have been reported.

Local

The local pain which may occur during the induction phase can be minimised by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<https://sideeffects.health.gov.il>).

4.9 Overdose

Accidental overdosage 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.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics

ATC code N01AX10

Mechanism of action

Propofol (2,6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The

mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABA_A receptors.

Pharmacodynamic effects

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Propofol-Lipuro 2% is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of Propofol-Lipuro 2%, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

Propofol-Lipuro 2% reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Clinical efficacy and safety

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

In general, there is less post-operative nausea and vomiting following anaesthesia with Propofol-Lipuro 2% than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.

Propofol-Lipuro 2%, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

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.

5.2 Pharmacokinetic properties

Absorption

When Propofol-Lipuro 2% is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate.

Distribution

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5-2 litres/minute).

Elimination

The decline in propofol concentrations following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2–4 minutes), rapid elimination (half-life 30-60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates < 1 month old (n = 25) (20 ml/kg/min) compared to older children (n = 36, age range 4 months – 7 years). Additionally inter-individual varia-

bility was considerable in neonates (range 3.7 – 78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4 – 24 months) (n = 8), 38.7 mL/min/kg (11 – 43 months) (n = 6), 48 ml/min/kg (1 – 3 years) (n = 12), 28.2 ml/min/kg (4 – 7 years) (n = 10) as compared with 23.6 ml/min/kg in adults (n = 6).

Linearity

The pharmacokinetics are linear over the recommended range of infusion rates of Propofol 2%.

5.3 Preclinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies.

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. In neonatal primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. The clinical significance of these nonclinical findings isn't known, and healthcare providers should balance the benefits of appropriate anaesthesia in young children less than 3 years of age and pregnant women who require procedures against the potential risks suggested by the preclinical data.

6 Pharmaceutical Particulars

6.1 List of excipients:

Soya-bean oil, refined,
Medium-chain triglycerides,
Glycerol,
Egg phospholipid for injection,
Sodium oleate,
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as Propofol-Lipuro 2% without prior flushing.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution

Propofol-Lipuro 2% should not be diluted.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze.

Keep vials in outer carton in order to protect from light.

6.5 Nature and contents of container

Glass vials are made of colourless glass (type II) according to Pharm. Eur. The vials are sealed with bromobutyl rubber closure and aluminium caps.

This product is supplied in glass vials of 50 ml, pack sizes: 1 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

In-use precautions:

Containers should be shaken before use.

For single use only. Any portion of the contents remaining after use should be discarded.

If two layers can be seen after shaking or if it is not milky-white the medicinal product should not be used.

Propofol-Lipuro 2% must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol-Lipuro 2% 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.

7 MANUFACTURER :

B. Braun Melsungen AG
Carl Braun St.D-34212 Melsungen, Germany

8 REGISTRATION HOLDER:

Lapidot Medical Import and Marketing Ltd.
8 Hashita street, Industrial Park, Caesarea 38900, ISRAEL.

9 MARKETING AUTHORISATION NUMBER:

141-66-31763-00

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