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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propofol-Lipuro 1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol-Lipuro 1 % contains

	per 1 ml	per 20 ml ampoule	per 50 ml vial	per 100 ml vial
Propofol	10 mg	200 mg	500 mg	1000 mg

Excipients with known effect:

1 ml of emulsion for injection or infusion contains
Soya-bean oil, refined 50 mg
Sodium oleate 0.03 mg

For the 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 1% is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children > 1 month
- 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 > 1 month.

4.2 Posology and Method of Administration

General instructions

Propofol-Lipuro 1% 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 1% 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 1%

Posology

Propofol-Lipuro 1% is given intravenously. The dosage is adjusted individually according to the patient's response.

- *General anaesthesia in adults*

Induction of anaesthesia:
For induction of anaesthesia Propofol-Lipuro 1% 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/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 1% may be reduced to a minimum of 1 mg/kg body weight. In these patients lower rates of administration should be applied (approximately 2 ml, corresponding to 20 mg every 10 seconds).

Maintenance of anaesthesia:
Anaesthesia can be maintained by administering Propofol-Lipuro 1% either 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% to 50 mg (5.0 ml Propofol-Lipuro 1% may be given according to clinical requirements. For maintenance of anaesthesia 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 be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

- *General anaesthesia in children over 1 month of age*

Induction of anaesthesia:
For induction of anaesthesia Propofol-Lipuro 1% should be slowly titrated against the patient's response 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, dose requirements may be higher (2.5 – 4 mg/kg body weight).

Maintenance of general anaesthesia:
Anaesthesia can be maintained by administering Propofol-Lipuro 1% by infusion or repeated bolus injection 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 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 mg/kg/h of propofol (see also section 4.4).

Propofol is not indicated for sedation in intensive care of patients of 16 years of age or younger (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 1% infusion to the desired level of sedation. Most patients will require 1.5 – 4.5 mg/kg body weight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg (1 – 2 ml Propofol-Lipuro 1% if a rapid increase of the depth of sedation is required.

In patients older than 55 years and in patients of ASA grades III and IV lower doses of Propofol-Lipuro 1% may be required and the rate of administration may need to be reduced.

- *Sedation for diagnostic and surgical procedures in children over 1 month 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 Propofol-Lipuro 1% as infusion to the desired level of sedation. Most patients require 1.5 – 9 mg/kg/h of propofol. The infusion may be supplemented by bolus administration of up to 1 mg/kg b.w. if a rapid increase of depth of sedation is required.

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

Method and duration of administration

- *Method of administration*

Intravenous use
Propofol-Lipuro 1% 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 (see also section 6.6).

Containers should be shaken before use.

Before use, the neck of the ampoule or 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 10 mg/ml contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol-Lipuro 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 vial seal. Administration must commence without delay. Asepsis must be maintained for both Propofol-Lipuro 10 mg/ml and the infusion equipment throughout the infusion period.

Any medicinal products or fluids added to a running Propofol-Lipuro 10 mg/ml infusion must be administered close to the cannula site. If infusion sets with filters are to be used, these must be lipid-permeable. Propofol-Lipuro 1 % (10 mg/ml) must not be administered via infusion sets with microbiological filters.

The contents of one ampoule or one vial of Propofol-Lipuro 10 mg/ml and any syringe containing Propofol-Lipuro 10 mg/ml are for **single use** in **one** patient.

<u>Infusion of undiluted Propofol-Lipuro 1%</u>

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

Infusion of diluted Propofol-Lipuro 1%
For administering infusion of diluted Propofol-Lipuro 1%, 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%.
The maximum dilution must not exceed 1 part of Propofol-Lipuro10 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% may be mixed with preservative-free lidocaine injection 1 % (mix 20 parts of Propofol-Lipuro 1% with up to 1 part of lidocaine injection 1%).

Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-Lipuro 10 mg/ml through the same intravenous line, it is recommended that the line 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 1% can be administered for a maximum period of 7 days.

4.3 Contraindications

Propofol-Lipuro 1% is contraindicated in patients with a known hypersensitivity to propofol or to any of the excipients.

Propofol-Lipuro 1% contains soya-bean oil and should not be used in patients who are hypersensitive to peanut or soya.

Propofol-Lipuro 1% must not be used in patients of 16 years of age or younger for sedation for intensive care (see section 4.4).

4.4 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 and dependence on propofol, predominantly by health care professionals, have 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.
Propofol clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce propofol clearance

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 vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of propofol.
During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.
Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When propofol is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that propofol is administered following the analgesic and the dose should be carefully titrated to the patient's response .
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 during the period of anaesthetic maintenance.

When propofol 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.

As with other anaesthetics, sexual disinhibition may occur during recovery

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 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 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, 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 (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 promptly consider decreasing or stopping the propofol dosage 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 10 mg/ml contains 0.1 g of fat.

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 1% 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 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'.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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.

Profound hypotension has been reported following anaesthetic induction 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.

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 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 can, however, be used during an induced abortion.
Obstetrics
propofol crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary

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.

4.7 Effects on the Ability to Drive and Use Machines

Propofol 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 induced impairment is not generally detectable beyond 12 hours (please see section 4.4).

4.8 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 and drug dependence (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
	Frequency not known (9)	Respiratory depression (dose dependent)
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)
	Very rare	Tissue necrosis (10) following accidental extravascular administration (11)
	Frequency not known (9)	Local pain, swelling following accidental extravascular administration
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 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 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 of propofol anaesthesia can be minimised by the co-administration of lidocaine and 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
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Mechanism of action, pharmacodynamic effect
After intravenous injection of Propofol-Lipuro 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.

5.2 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 been calculated as 2 – 4 minutes.

During elimination the decline of blood levels is slower. The elimination half-life during the β-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.

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 urine.

Paediatric population

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 variability 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).

5.3 Preclinical Safety Data

Preclinical data reveal no specific hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted.

Reproductive toxicity studies have shown effects related to pharmacodynamic properties of propofol only at high doses. Teratogenic effects have not been observed.

In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Soya-bean oil, refined,
medium-chain triglycerides,
glycerol,
egg lecithin,
sodium oleate,
water for injections.

6.2 Incompatibilities

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

6.3 Shelf Life

2 years.

After first opening:
to be used immediately.

After dilution according to directions:
aAdministration of dilution must commence immediately after preparation.

6.4 Special Precautions for Storage

Do not store above 25 °C.
Do not freeze.
Keep the ampoules and vials in the outer carton in order to protect from light.

6.5 Nature and Contents of Container

Colourless Type I glass ampoules containing 20 ml of emulsion.

Colourless Type II glass vials sealed with bromobutyl rubber stoppers containing 50 ml or 100 ml of emulsion.

Pack sizes:

glass ampoules :	5 x 20 ml
glass vials:	10 x 20 ml, 1 x 50 ml, 10 x 50 ml, 1 x 100 ml, 10 x 100 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlings

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

Containers should be shaken before use.

For single use only. Any portion of contents remaining after use must be discarded, see section 4.2.

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

Propofol-Lipuro 1% should only be mixed with the following products: glucose 50 mg/ml (5 % w/v) solution, sodium chloride 9 mg/ml (0.9% w/v) solution, or sodium chloride 1.8 mg/ml (0.18 %) and glucose 40 mg/ml (4 % w/v) solution, and preservative-free lidocaine injection 1% (see section 4.2 "Method and duration of administration" "Infusion of diluted Propofol-Lipuro 1%“)

Co-administration of Propofol-Lipuro 1% together with glucose solution 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 Registration numbers:

127 87 30672 00

127 87 30672 11

8 Manufacturer:

B.Braun Melsungen AG
34212 Melsungen
Germany

9 License holder:

Lapidot Medical Import and Marketing Ltd.

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