Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Propofol-Lipuro 0.5% (5 mg/ml) emulsion for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion for injection or infusion contains 5 mg propofol.
1 ampoule with 20 ml contains 100 mg propofol

Excipients with known effect
1 ml of emulsion contains
Soya-bean oil refined 50 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 0.5% (5 mg/ml) is a short-acting intravenous general anaesthetic indicated for

- induction of general anaesthesia in adults and children > 1 month
- induction of sedation for diagnostic and surgical procedures in adults and children > 1 month
- short term sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia, in adults.

4.2 Posology and method of administration

General instructions
Propofol-Lipuro 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 oximeter) 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 should not be given by the same person that carries out the surgical or diagnostic procedure.

Propofol-Lipuro 0.5% (5 mg/ml) is intended for use in children, adolescents and adults, especially the pain-sensitive ones, because of the lower pain on injection compared to higher strengths.

Supplementary analgesic medicinal products are generally required in addition to Propofol-Lipuro

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

- *Induction of general anaesthesia in adults*

For induction of anaesthesia Propofol-Lipuro 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 per kg body weight. Repeat bolus injections may be given according to clinical requirements.

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 propofol dose may be reduced to a minimum of 1 mg/kg body weight. In these patients lower rates of administration should be applied (approximately 4 ml of Propofol-Lipuro, corresponding to 20 mg of propofol every 10 seconds).

- *Induction of general anaesthesia in children over 1 month of age*

For induction of anaesthesia Propofol-Lipuro 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 of propofol per kg body weight for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirement may be higher (2.5-4 mg of propofol per kg body weight).

Propofol-Lipuro 0.5% (5 mg/ml) is contraindicated to be used for maintenance of anaesthesia (see also section 4.3)

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

- *Short-term sedation and induction of 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 of propofol per kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol-Lipuro to the desired level, using e.g. a syringe pump. Most patients will require 1.5-4.5 mg of propofol per kg body weight per hour. Additional boluses of 10-20 mg of propofol (2-4 ml of Propofol-Lipuro 5 mg/ml) may be given 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 may be required and the rate of administration may need to be reduced.

- *Induction of 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.

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

Method and duration of administration

- *Method of administration*

Intravenous use
Propofol-Lipuro is administered undiluted by injection or by continuous infusion after dilution with glucose 50 mg/ml (5% w/v) solution or sodium chloride 9 mg/ml (0.9% w/v) solution (see also section 6.6).

Containers should be shaken before use.

Before use, the neck of the ampoule should be cleaned with medicinal alcohol (spray or swabs). After use, tapped containers must be discarded.

Propofol-Lipuro contains no antimicrobial preservatives and supports growth of microorganisms. Therefore, Propofol-Lipuro is to be drawn up aseptically into a sterile syringe immediately after opening the ampoule. Administration must commence without delay. Asepsis must be maintained for both Propofol-Lipuro and administration equipment throughout the entire period of administration.

The contents of one ampoule of Propofol-Lipuro and any syringe containing Propofol-Lipuro are for single use in one patient.

Any medicinal products or fluids added to a running Propofol-Lipuro infusion must be administered close to the cannula site. If infusion sets with filters are to be used, these must be lipid-permeable.

Administration of undiluted Propofol-Lipuro
When administering Propofol-Lipuro by continuous infusion, administration rates should always be controlled by appropriate apparatus, e.g. a syringe pump. Any portion of Propofol-Lipuro remaining after the end of administration must be discarded.

Infusion of diluted Propofol-Lipuro
For infusion of diluted Propofol-Lipuro, 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.

The maximum dilution must not exceed 1 part of Propofol-Lipuro with 4 parts of glucose 50 mg/ml (5% w/v) solution or sodium chloride 9 mg/ml (0.9% w/v) solution (minimum concentration 1 mg propofol/ml).

The mixture should be prepared aseptically immediately prior to administration.

The pain on initial injection may be reduced by adding lidocaine to Propofol-Lipuro: One part of preservative-free lidocaine injection 10 mg/ml (1%) may be added to 40 parts of Propofol-Lipuro.

Before giving the muscle relaxants atracurium or mivacurium subsequent to Propofol-Lipuro through the same intravenous line, it is recommended that the line be rinsed prior to administration.

- *Duration of administration*

Propofol-Lipuro 0.5% (5 mg/ml) can be administered for a maximum period of 1 hour.

4.3 Contraindications

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

Propofol-Lipuro 0.5% (5 mg/ml) is contraindicated:

- for maintenance of general anaesthesia
- for maintenance of sedation for diagnostic and surgical procedures in children
- for sedation for intensive careSafety and efficacy for these indications have not been demonstrated.

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.

In case of repeated boluses for induction of anaesthesia the maximum fat administration should not exceed 150 mg fat/kg/h which corresponds to 1.5 ml/kg/h of Propofol-Lipuro.

As with other sedative agents, when propofol is used for short-term 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 also section 4.2).

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 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.

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.

Patients with hypoproteinaemia might have a higher risk to obtain adverse events based on a higher fraction of unbound propofol. Dose reduction in these patients is recommended.

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

Use of propofol for ICU sedation (see section 4.3) has been associated with a constellation of metabolic disturbances 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 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 oxy-gen 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 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.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.
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 0.5% (5 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 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. Administration must commence without delay. Asepsis must be maintained for both propofol and infusion equipment throughout the infusion period.

This medicinal product contains less than 1 mmol sodium (23 mg) per 20 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Propofol has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking medicinal products, inhalational medicinal products and analgesic medicinal products; 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.

The concurrent administration of other CNS depressants such as pre-medication medicinal products, inhalation medicinal products, analgesic medicinal products may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol. Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

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
The safety of propofol during pregnancy has not been established.
Studies in animals have shown reproductive toxicity (see section 5.3).
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 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.

Fertility
No data available.

4.7 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 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 up to anaphylactic shock – may include angioedema, bronchospasm, erythema and

		hypotension
Metabolism and nutritional disorders:	Frequency not known (9)	Metabolic acidosis (5), hyperkalaemia (5), hyperlipidaemia (5)
Psychiatric disorders:	Very rare (< 1/10 000)	Sexual disinhibition
	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 arrest, cardiac failure (5), (7)
Vascular disorders:	Common (≥ 1/100, < 1/10)	Hypotension (2)
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)
Reproductive system and breast disorders:	Frequency not known (9)	Priapism
Renal and urinary disorders	Very rare (< 1/10 000)	Discolouration of urine following prolonged administration
	Frequency not known (9)	Renal failure (5)
General disorders and administration site conditions:	Very common (≥ 1/10)	Local pain on induction (4)
	Uncommon (≥ 1/1000, < 1/100)	Injection site thrombosis and injection site phlebitis
	Very rare (< 1/10 000)	Tissue necrosis (10) following accidental extravascular administration (11)
	Frequency not known (9)	Local pain, swelling, and inflammation following accidental extravascular administration (11)
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 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.
[11] Treatment is symptomatic and may include immobilisation and, if possible, elevation of affected limb, cooling, close observation, consultation of surgeon if necessary.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms
Accidental overdose is likely to cause cardiorespiratory depression.

Treatment
Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of 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, pharmacodynamic effect
After intravenous injection of Propofol-Lipuro, 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 rationale for development of Propofol-Lipuro 0.5% (5 mg/ml) was the reduction of pain at injection site; this was clearly demonstrated in two clinical studies, one in children and one in adults.

The formulation of propofol in a mixed medium- and long-chain triglyceride emulsion leads to lower concentrations of free propofol 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 0.5% (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

Absorption
After intravenous administration about 98% of propofol is bound to plasma protein.

Distribution
After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (a-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 b-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 metabolised 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 paediatric patients 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.

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. The clinical significance of these nonclinical findings is not known.. 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 phospholipids 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.

6.3 Shelf life

2 years.

After first opening: to be used immediately.

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

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.

6.5 Nature and contents of container

This medicinal product is supplied in glass ampoules of 20 ml.

Glass ampoules are made of colourless glass (type I) according to Ph. Eur..

Pack sizes:
Glass ampoules: 5 x 20 ml

6.6 Special precautions for disposal and other handling

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

Containers should be shaken before use.

For single use in one patient only. Any portion of contents remaining after first use must be discarded.

If two layers can be seen after shaking, the product should not be used.

Propofol-Lipuro should only be mixed with the following products: glucose 50 mg/ml (5% w/v) solution for infusion, sodium chloride 9 mg/ml (0.9% w/v) solution for infusion and preservative-free lidocaine 10 mg/ml (1%) solution for injection (refer to section 4.2, subsection "Infusion of diluted Propofol-Lipuro")

Co-administration of Propofol-Lipuro together with glucose 50 mg/ml (5% w/v) solution for infusion or sodium chloride 9 mg/ml (0.9% w/v) solution for infusion via a Y-connector close to the injection site is possible.

7 MARKETING AUTHORISATION HOLDER

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Carl-Braun-Straße 1
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8 MARKETING AUTHORISATION NUMBER

PA0736/018/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristation: 21st July 2008
Date of last renewal: 5th June 2013

10 DATE OF REVISION OF THE TEXT

May 2022