SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propofol 1% (10 mg/ml) emulsion for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml emulsion contains 10 mg propofol.

Each 10 ml pre-filled syringe contains 100 mg propofol.
Each 20 ml pre-filled syringe contains 200 mg propofol.
Each 50 ml pre-filled syringe contains 500 mg propofol.

Excipients with known effect:
Each ml emulsion contains:

soya-bean oil, refined	50 mg
sodium	max. 0.06 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection/infusion in pre-filled syringe
White oil-in-water emulsion

pH of emulsion: 7.5 – 8.5
Osmolality of emulsion: 300 mosmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 1% is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults, adolescents and children > 1 month
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults, adolescents and children > 1 month
- sedation of ventilated patients > 16 years of age in the intensive care unit

4.2 Posology and method of administration

Propofol 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 oxymetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.
For sedation during surgical and diagnostic procedures Propofol 1% should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Propofol 1% should be individualised based on the response of the patient and premedications used.

Supplementary analgesic agents are generally required in addition to Propofol 1%.

Posology

General anaesthesia in adults

Induction of anaesthesia:
For induction of anaesthesia Propofol 1% should be titrated (approximately 20 - 40 mg propofol every 10 seconds) against the response of the patient until clinical signs show the onset of anaesthesia.

Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg propofol/kg bodyweight.

In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Propofol 1% may be reduced to a minimum of 1 mg propofol/kg bodyweight. Lower rates of administration of Propofol 1% should be used (approximately 2 ml of the 10 mg/ml emulsion (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 1% either by continuous infusion or repeat bolus injections.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg bodyweight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg bodyweight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

In elderly patients, patients in unstable general conditions, patients with impaired cardiac function or hypovolaemic patients and patients of ASA grades III and IV the dosage of Propofol 1% may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

For maintenance of anaesthesia with Propofol 1% using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 – 5 ml Propofol 1%) should be given according to clinical requirements.

Rapid bolus administration (single or repeated) with Propofol 1% should not be used in the elderly as this may lead to cardiopulmonary depression.

General anaesthesia in children over 1 month of age

Induction of anaesthesia:

For induction of anaesthesia Propofol 1% should be titrated slowly until clinical signs show the onset of anaesthesia.
The dose should be adjusted according to age and/or bodyweight. Most patients over 8 years of age require approximately 2.5 mg/kg bodyweight Propofol 1% 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 bodyweight).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering Propofol 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 for diagnostic and surgical procedures in adult patients

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 - 1 mg propofol/kg bodyweight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% infusion to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg bodyweight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg propofol (1 – 2 ml Propofol 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 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 bodyweight propofol for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol 1% infusion to the desired level of sedation. Most patients require 1.5 - 9 mg/kg/h propofol. With Propofol 1% 10mg/ml, the infusion may be supplemented by bolus administration of up to 1 mg/kg bodyweight if a rapid increase of depth of sedation is required.

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

Sedation in patients over 16 years of age in the intensive care unit

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Propofol 1% should be given by continuous infusion. The dose should be adjusted according to the depth of sedation required. Usually satisfactory sedation is achieved with administration rates in the range of 0.3 to 4.0 mg propofol/kg bodyweight/h. Rates of infusion greater than 4.0 mg propofol/kg bodyweight/h are not recommended (see section 4.4).

Administration of propofol by a target controlled infusion (TCI) system is not advised for sedation in the intensive care unit (ICU).

Duration of administration

The duration of administration must not exceed 7 days.

Method of administration

For intravenous use.
For single use only. Any unused emulsion must be discarded.

Pre-filled syringes should be shaken before use.
If two layers can be seen after shaking the emulsion should not be used.
Use only homogeneous preparations and undamaged pre-filled syringes.

Propofol 1% can be used for infusion undiluted or diluted (for dilution see section 6.6).

When Propofol 1% is infused , it is recommended that equipment such as burettes, drop counter, syringe pumps (including TCI systems) or volumetric infusion pumps should always be used to control infusion rates.

Propofol 1% is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of micro-organisms.
The emulsion must be drawn aseptically into a giving set immediately after opening the syringe. Administration must commence without delay.

Asepsis must be maintained for both Propofol 1% and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Propofol 1% infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve. For instructions on co-administration of the medicinal product, see section 6.6.

Propofol 1% must not be administered via a microbiological filter.
Propofol 1% and any infusion equipment containing Propofol 1% are for **single** administration in an **individual** patient. After use remaining solution of Propofol 1% has to be discarded.

Infusion of undiluted Propofol 1%:
As usual for fat emulsions, the infusion of undiluted Propofol 1% via one infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Propofol 1% must be discarded or replaced if necessary.

Infusion of diluted Propofol 1%:
For administering infusion of diluted Propofol 1%, burettes, drop counters or 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 1%. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

To reduce pain on the injection site, lidocaine may be injected immediately before the use of Propofol 1% (see section 4.4). Alternatively, Propofol 1% may be mixed, immediately for use, with preservative free lidocaine injection (20 parts of Propofol 1% with up to 1 part of 1 % lidocaine injection solution under controlled and validated aseptical conditions. The mixture has to be administered within 6 hours after preparation.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Propofol 1%.

Propofol 1% will be injected into a vein either manually or by electric pumps. In case of using electronic pumps, appropriate compatibility should be ensured.

10 ml and 20 ml glass syringes and 10 ml plastic syringes are suitable for manual use only and must not be used with a pump.
10 ml and 20 ml glass syringes must also not be used with needle-free connectors, except standard tubing or 3-way stopcocks to avoid breakage or clogging of the connector.
If breakage/clogging are observed, the pre-filled syringe must be disposed and a new one must be used.

Application of pre-filled syringes (for pre-assembled syringes step 2 can be omitted):
Sterility has to be ensured. The outer surface of the syringe and the plunger rod are not sterile.

1) Take out the syringe from the packaging and shake it.
2) Insert the plunger rod by screwing it clock-wise into the syringe.
3) Remove the tip cap from the syringe and connect the infusion line, needle or cannula to the syringe. Get rid of the air bubble (a small bubble can remain) and the ready-to-use syringe will be installed in the pump or administered manually.

Target Controlled Infusion – Administration of Propofol 1% by pumps (for 20 ml plastic and 50 ml plastic syringe only):

Administration of Propofol 1% by a Target Controlled Infusion system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures.

Propofol 1% may be administered by a Target Controlled Infusion system incorporating appropriate Target Controlled Infusion software. Users must be familiar with the infusion pump users' manual, and with the administration of Propofol 1% by Target Controlled Infusion.

The system allows the anaesthetist or intensivist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) plasma and/or effect-side concentrations of propofol.

Different modalities of the various pump systems should be considered i.e. the Target Controlled Infusion system might assume that the initial blood propofol concentration in the patient is zero. Therefore, in patients who have received prior propofol, there may be a need to select a lower initial target concentration when commencing Target Controlled Infusion. Similarly, the immediate recommencement of Target Controlled Infusion is not recommended if the pump has been switched off.

Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

Induction and Maintenance of General Anaesthesia during target controlled infusion

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4 – 8 microgram/ml. An initial target of 4 microgram/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 microgram/ml is advised. Induction time with these targets is generally within the range of 60–120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration can then be increased in steps of 0.5 – 1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3–6 microgram/ml usually maintain satisfactory anaesthesia.

The predicted propofol concentration on waking is generally in the region of 1.0 – 2.0 microgram/ml and will be influenced by the amount of analgesia given during maintenance.

Sedation during intensive care (target controlled infusion not advised)

Target blood propofol concentration settings in the range of 0.2 – 2.0 microgram/ml will generally be required. Administration should begin at low target setting which should be titrated against the response of the patient to achieve the depth of sedation desired.

4.3 Contraindications

Propofol is contraindicated in patients with a known hypersensitivity to propofol or any of the excipients listed in section 6.1.

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

Propofol 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.

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.)

Delayed epileptiform attacks may occur even in non-epileptic patients, the delay period ranging from a few hours to several days.

Special patient groups

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia
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 which reduces cardiac output will also reduce propofol clearance.**

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of propofol.

Propofol should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.

Due to a higher dosage in patients with severe overweight the risk of haemodynamic effects on the cardiovascular system should be taken into consideration.

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 a bradycardia.

Epilepsy
When propofol is administered to an epileptic patient, there may be a risk of convulsion.

In epileptic patients delayed epileptiform attacks may occur, the delay period ranging from a few hours to several days.

Before anaesthesia of an epileptic patient, it should be checked that the patient has received the antiepileptic treatment. Although several studies have demonstrated efficacy in treating status epilepticus, administration of propofol in epileptic patients may also increase the risk of seizure.

Use of propofol is not recommended with electroconvulsive therapy.

Patients with disorders of fat metabolism

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 a high intracranial pressure
Special care should be recognised in patients with a high intracranial pressure and a low mean arterial pressure as there is a risk of a significant decrease of the intracerebral perfusion pressure.

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 of the SmPC) 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 1% is not advised for general anaesthesia in children younger than 1 month of age.

Due to the limited data available, the use of target controlled infusion (TCI) in the paediatric population below 2 years of age cannot be recommended.

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 (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 the 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 1% contains approximately 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 1% contains no antimicrobial preservatives and supports growth of micro-organisms.

When propofol is to be aspirated, it must be drawn aseptically into a giving set immediately after opening the syringe. 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.

Pain on the injection site
To reduce pain on the injection site during induction of anaesthesia with Propofol 1%, lidocaine can be injected prior to the propofol emulsion (see section 4.2).
Intravenous lidocaine must not be used in patients with hereditary acute porphyria.

This medicinal product contains less than 1 mmol (23 mg) sodium per 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.

Concomitant use of benzodiazepines, parasympatholytic agents or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

A need for lower propofol doses has been observed in patients taking midazolam. The co-administration of propofol with midazolam is likely to result in enhanced sedation and respiratory depression. When used concomitantly, a dose reduction of propofol should to be considered.

After additional premedication with opioids, the sedative effects of propofol may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea.

It should be taken into consideration that concomitant use of propofol and medicinal products for premedication, inhalation agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects.
Concomitant use of central nervous system depressants (e.g. alcohol, general anaesthetics, narcotic analgesics) will result in intensification of their sedative effects. When Propofol 1% is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur.

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmine.

Leucoencephalopathy has been reported with administration of lipid emulsions as used for Propofol 1% in patients receiving cyclosporine.

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. Propofol should not be given to pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Propofol can, however, be used during an induced abortion.
High doses (more than 2.5 mg propofol/kg bodyweight for induction or 6 mg propofol/kg bodyweight/h for maintenance of anaesthesia) should be avoided.

Studies in animals have shown reproductive toxicity (see section 5.3)

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 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
After administration of Propofol 1%, the patient should be kept under observation for an appropriate period of time. The patient should be instructed not to drive, operate machinery, or work in potentially hazardous situations. The patient should not be allowed to go home unaccompanied, and should be instructed to avoid consumption of alcohol.

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, sexual disinhibition. 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. Vertigo, shivering and sensation of cold during recovery
	Very rare (<1/10 000)	Postoperative unconsciousness
	Frequency not known [9]	Involuntary movements
Cardiac disorders:	Common (>1/100, <1/10)	Bradycardia [1] and tachycardia during induction
	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, coughing and singultus during induction
	Frequency not known [9]	Respiratory depression (dose dependant)

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 disorders	Not known	Priapism
General disorders and administration site conditions:	Very common (>1/10)	Local pain on induction [4]
	Very rare (<1/10 000)	Tissue necrosis [10] following accidental extravascular administration
	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 1 % 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.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 of the patient's head and, if severe, use of plasma expanders and pressor agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics; Other general anaesthetics
ATC-Code: N01AX10

Mechanism of action/Pharmacodynamic effects

Propofol (2,6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action. 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 and lasts, depending on the metabolism and elimination, 4 to 6 minutes.

Clinical efficacy and safety

Under the usual maintenance regimen significant accumulation with either repeated injections or infusions of propofol has not been seen. Patients recover consciousness rapidly.

Bradycardia and hypotension reported during induction of anaesthesia may be caused by a cerebral vagotonic effect or inhibition of sympathetic activity. However, haemodynamics generally reverts to normal during maintenance of anaesthesia.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption

Propofol is bound to plasma proteins for 98%. Following intravenous administration the pharmacokinetics of propofol can be described by a 3-compartment model.

Distribution/ Biotransformation/Elimination

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

Due to the limited data available, the use of target controlled infusion (TCI) in the paediatric population below 2 years of age cannot be recommended.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted. Teratogenic effects have not been observed. In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site, paravenous and subcutaneous injection induced histological reactions marked by inflammatory infiltration and focal fibrosis.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
Medium-chain triglycerides
Purified egg phosphatides
Glycerol
Oleic acid
Sodium hydroxide
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

Shelf life of the medicinal product in its original package before opening: 2 years.

Shelf life after first opening: Medicinal product must be used immediately after first opening. Administration systems with undiluted Propofol 1% should be replaced after 12 hours.

Shelf life after dilution: Medicinal product must be used immediately after dilution. The administration should be completed within 6 hours after dilution.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 or 20 mL pre-filled syringe (glass, hydrolytic class 1) with brombutyl tip cap, brombutyl plunger and PP piston rod
10 or 20 ml pre-filled syringe (cyclo-olefine-copolymer) with bromobutyl tip cap, bromobutyl plunger and PP piston rod
50 ml pre-filled syringe (cyclo-olefine-copolymer) with bromobutyl tip cap, bromobutyl plunger and PP piston rod

Packs containing 5 glass syringes with 10 ml emulsion.
Packs containing 6 plastic syringes with 10 ml emulsion.
Packs containing 5 glass syringes with 20 ml emulsion.
Packs containing 6 plastic syringes with 20 ml emulsion.
Packs containing 1 plastic syringe with 50 ml emulsion.

6.6 Special precautions for disposal

Propofol 1% should not be mixed prior to administration with injection or infusion solutions other than glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection or preservative free lidocaine 10 mg/ml (1%) solution for injection. The maximum dilution must not exceed 1 part of Propofol 1% with 4 parts of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 6 hours after preparation (see also section 4.2.).
Final propofol concentration must not be below 2 mg/ml.
Co-administration of a glucose 50 mg/ml (5 %) solution for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection or sodium chloride 1.8 mg/ml (0.18 %) solution for injection and glucose 40 mg/ml (4 %) solution for injection with Propofol 1% is permitted via a Y-piece connector close to the injection site.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi
Cestrian Court, Eastgate Way, Manor Park,
Runcorn
Cheshire
WA7 1NT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0239

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/04/2013

10 DATE OF REVISION OF THE TEXT

10/11/2023