SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propofol 1 % (10 mg/1 ml) Fresenius emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion contains 10 mg propofol.
Each 20 ml ampoule contains 200 mg propofol.
Each 50 ml vial contains 500 mg propofol.
Each 100 ml vial contains 1000 mg propofol.

Excipients with known effect:
1 ml emulsion contains:

soya-bean oil, refined	100 mg
sodium	max. 0.06 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection or infusion

White oil-in-water emulsion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 1 % (10 mg/1 ml) Fresenius is a short-acting intravenous general anaesthetic for

- induction and maintenance of general anaesthesia in adults and children >1 month
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults 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 Fresenius 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 Fresenius should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Propofol Fresenius emulsion should be individualised based on the response of the patient and premedications used.
Supplementary analgesic agents are generally required in addition to Propofol Fresenius.

Posology

General anaesthesia in adults

Induction of anaesthesia:

For induction of anaesthesia Propofol Fresenius 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 Fresenius may be reduced to a minimum of 1 mg propofol/kg bodyweight. Lower rates of administration of Propofol 1 % (10 mg/1 ml) Fresenius should be used (approximately 2 ml (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Propofol 1 % (10 mg/1 ml) Fresenius 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 Fresenius may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

For maintenance of anaesthesia using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 - 5 ml Propofol 1 % (10 mg/1 ml) Fresenius) should be given according to clinical requirements.

Rapid bolus administration (single or repeated) 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 Fresenius 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 Fresenius 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 Fresenius 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 Fresenius 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 % (10 mg/1 ml) Fresenius) 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 Fresenius 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 Fresenius infusion to the desired level of sedation. Most patients require 1.5 - 9 mg/kg/h propofol. 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 Fresenius 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).

Method of administration

For intravenous use.

Propofol 1 % (10 mg/1 ml) Fresenius can be used for infusion undiluted or diluted with 5% w/v glucose intravenous infusion solution or 0.9% w/v sodium chloride intravenous infusion solution only, in glass infusion bottles.

When Propofol 1 % (10 mg/1 ml) Fresenius is infused undiluted, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

Containers should be shaken before use.

Use only homogeneous preparations and undamaged containers.

Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

Propofol Fresenius is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of micro-organisms.

The emulsion must be drawn aseptically into a sterile syringe and giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay.

Asepsis must be maintained for both Propofol Fresenius and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Propofol Fresenius infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve.

Propofol Fresenius must not be mixed with other solutions for infusion or injection. But 5 % w/v glucose solution, 0.9 % w/v sodium chloride solution or 0.18% w/v sodium chloride and 4 % w/v glucose solution may be administered via suitable appendages at the cannula site.

Propofol Fresenius must not be administered via a microbiological filter.

Propofol Fresenius and any infusion equipment containing Propofol Fresenius are for **single** administration in an **individual** patient. After use remaining solution of Propofol Fresenius has to be discarded.

Infusion of undiluted Propofol 1 % (10 mg/1 ml) Fresenius:

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

Infusion of diluted Propofol 1 % (10 mg/1 ml) Fresenius:

For administering infusion of diluted Propofol 1 % (10 mg/1 ml) Fresenius, burettes, drop counters 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 1 % (10 mg/1 ml) Fresenius. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

The maximum dilution must not exceed 1 part of Propofol 1 % (10 mg/1 ml) Fresenius with 4 parts of 5 % w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration 2 mg propofol per 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.

Propofol 1 % (10 mg/1 ml) Fresenius must not be mixed with other solutions for infusion or injection. However, co-administration of a 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 with Propofol 1 % (10 mg/1 ml) Fresenius is permitted via a Y-piece connector close to the injection site.

To reduce pain on the injection site, lidocaine may be injected immediately before the use of Propofol 1 % (10 mg/1 ml) Fresenius (see section 4.4). Alternatively, Propofol 1 % (10 mg/1 ml) Fresenius may be mixed, immediately for use, with preservative free lidocaine injection (20 parts of Propofol 1 % (10 mg/1 ml) Fresenius 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 Fresenius.

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

The duration of administration must not exceed 7 days.

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 Fresenius 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.

Fresenius Propoven 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 Fresenius Propoven 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.

Fresenius Propoven 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 and 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.

Pain on the injection site

To reduce pain on the injection site during induction of anaesthesia with Fresenius Propoven 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 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 Fresenius 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 Fresenius 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 Fresenius, 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] Hepatitis[11], acute hepatic failure[11]
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.

[11] After both long- and short-term treatment and in patients without underlying risk factors.

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: Other anaesthetics
ATC-Code: NO1AX10

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.

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 revert to normal during maintenance of anaesthesia.

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

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

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).

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.

Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life but may extend out to approximately 3 years of age in humans. In neonatal primates, exposure to 3 hours of an

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
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

The shelf life of the product in its original package is 3 years.

Administration systems with undiluted Propofol Fresenius should be replaced after 12 hours.

Dilutions with 5 % w/v glucose solution or 0.9 % w/v sodium chloride solution or an admixture with 1 % preservative free lidocaine injection solution (at least 2 mg propofol per ml) should be prepared aseptically (controlled and validated conditions preserved) immediately before administration and administration should be completed within 6 hours after dilution.

After opening the product must be used immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Colourless glass ampoule(s) (type I) of 20 ml
Colourless glass vial(s) (type II) of 50 ml with a bromobutyl rubber closure
Colourless glass vial(s) (type II) of 100 ml with a bromobutyl rubber closure
Packs containing 5 glass ampoules with 20 ml emulsion
Packs containing 10 glass ampoules with 20 ml emulsion
Packs containing 1 glass vial with 50 or 100 ml emulsion
Packs containing 10 glass vials with 50 or 100 ml emulsion
Packs containing 15 glass vials with 50 or 100 ml emulsion

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Propofol 1 % (10 mg/1 ml) Fresenius should not be mixed prior to administration with injection or infusion solutions other than 5 % w/v glucose solution or 0.9 % w/v sodium chloride solution or 1 % preservative free lidocaine injection solution (see also section 4.2). Final propofol concentration must not be below 2 mg/ml.

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

Containers 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 containers.

Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
Cestrian Court
Eastgate Way
Manor Park
Runcorn
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WA7 1NT

8 MARKETING AUTHORISATION NUMBER

PL 08828/0144

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/10/2010

10 DATE OF REVISION OF THE TEXT

26/09/2024