Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Propofol 20 mg/ml Emulsion for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of emulsion for injection/infusion contains 20 mg of propofol.
Each 50 ml vial contains 1000 mg of propofol

Excipient with known effect:
Each ml of emulsion for injection/infusion contains: Soya bean oil refined 50 mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Emulsion for injection/infusion.
White milky oil-in-water emulsion.

Osmolality: 250 to 390 mOsm/Kg.

pH between 6.00 and 8.50

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol 20 mg/ml is a short-acting intravenous anaesthetic for the
- induction and maintenance of anaesthesia in adults and children over 3 years of age,
-sedation of ventilated patients over 16 years of age during intensive care,
- sedation of adults and children over 3 years of age for surgical and diagnostic procedures, alone or in combination with local or regional anaesthesia.

4.2 Posology and method of administration

Propofol 20 mg/ml may only be administered by doctors that have been trained in anaesthesiology or intensive care. Sedation or anaesthesia with Propofol 20 mg/ml and the surgical or diagnostic procedure may not be performed by the same person.

The cardiac, circulatory and respiratory functions should be continuously monitored (e.g. ECG, pulse oxymetry). The customary equipment for possible accidents during anaesthesia or sedation must be ready for use at all times.

The dosage should be adjusted individually while taking the premedication and the patient's reaction into consideration.

Normally, the additional administration of analgesics is necessary.
Administration of boluses with Propofol 20 mg/ml is not recommended.

Anaesthesia for adults:
Induction of anaesthesia:
For induction of anaesthesia, Propofol 20 mg/ml is administered, titrated at a speed of 20 - 40 mg Propofol every 10 seconds, by means of an infusion pump until unconsciousness occurs.

Most adults less than 55 years of age would normally require a total dose of 1.5 - 2.5 mg propofol/kg of body weight.

For patients in risk groups ASA III and IV, especially in the case of prior cardiac damage and elderly patients, it may be necessary to reduce the total dosage of Propofol 20 mg/ml down to 1 mg Propofol/kg of bodymass, Whereby Propofol 20 mg/ml is administered at slower infusion speed (approximately 20 mg propofol every 10 seconds).

Maintenance of anaesthesia:
For maintenance of anaesthesia by means continuous infusion, the dosage and infusion speed must be adjusted for each individual.

Normally, the dosage is 4 -12 mg propofol/kg of body mass per hour in order to maintain a satisfactory level of anaesthesia. In the case of elderly patients, in a poor general state of health or with hypovolemia and patients in the risk groups ASA III and IV, the dosage of Propofol 20 mg/ml may be reduced down to 4 mg Propofol/kg of body mass per hour.

Anaesthesia in children from 3 years of age
Induction of anaesthesia
For the induction of anaesthesia, Propofol 20 mg/ml is titrated slowly until clinical signs can be seen that indicate the start of anaesthesia. The dose should be adjusted based on the age and/or body weight. Most children over 8 years of age require approximately 2.5 mg Propofol/kg of body mass for induction of anaesthesia. In the case of younger children, the required dose may be higher (2.5 - 4 mg Propofol/kg of body mass). Lower doses are recommended for patients in the risk groups ASA III and IV (see section 4.4).

Maintenance of anaesthesia
Maintenance of the required depth of anaesthesia can be achieved with the administration of Propofol 20 mg/ml by means of an infusion. The required dosage rates vary considerably among patients, however a satisfactory state of anaesthesia is normally achieved at doses in the range of 9 - 15 mg Propofol/kg of body mass per hour. In the case of younger children, the required dose may be higher.

Lower doses are recommended for patients in the risk groups ASA III and IV (see section 4.4).

There is not sufficient information available yet regarding use in children under 3 years of age.

Sedation of patients over 16 years of ageduring intensive care.
For the sedation of ventilated patients during intensive care,, Propofol 20 mg/ml should be administered as a continuous infusion. The dosage is based on the desired depth of sedation. Normally, the desired depths of sedation can be achieved with doses in the range of 0.3 to 4.0 mg propofol/kg of body mass per hour. (see section 4.4).

Propofol 20 mg/ml may not be used for the sedation of children aged 16 years or younger as part of intensive care.

The administration of Propofol 20 mg/ml by means of a TCI system is not recommended for sedation as part of intensive care.

Sedation of adults forsurgical and diagnosticprocedures.
During the administration of Propofol 20 mg/ml, the patient must be continually monitored for signs of a decrease in blood pressure, respiratory tract obstruction and oxygen deficiency and the customary emergency equipment for accidents must be kept ready.

For induction of anaesthesia, generally 0.5 – 1.0 mg propofol/kg of body mass are administered for 1 to 5 minutes. For themaintenance of anaesthesia, the dosage is determined based on the desired depth of sedation and is generally in the range between 1.5 - 4.5 mg propofol/kg of body massper hour.

A lower dosage and slower administration may be necessary for patients in risk groups ASA III and IV. A lower dosage may also be necessary in patients over 55 years of age.

Note
In the case of elderly patients, smaller doses are required for the induction of anaesthesia with Propofol 20 mg/ml. The patient's general state of health and age should be taken into account. The lowered dose should be administered more slowly and titrated according to the reaction.

Even when using Propofol 20 mg/ml for maintenance of anaesthesia and for sedation, the infusion rate and the selected Propofol concentration in the blood should be decreased. An additional lowering of the dosage and the infusion rate is necessary for patients in risk groups ASA III and IV. Elderly patients should not be given any bolus injections (individual or multiple), since circulatory and respiratory depression may result.

Sedation of children from 3 years of age for surgical and diagnostic procedures
The dosage and the periods between doses are selected based on the required depth of sedation and the clinical response. For the induction of sedation, a dose of 1 - 2 mg Propofol/kg of body weight is necessary for most paediatric patients.
Maintenance of sedation is achieved with the titration of Propofol 20 mg/ml via an infusion until the desired depth of sedation is reached. For most patients, 1.5 - 9 mg Propofol/kgof body mass per hour is required.

Lower doses may be necessary for patients in the risk groups ASA III and IV.

Propofol 20 mg/ml may not be used for the sedation of children aged 16 years or younger as part of intensive care.

Method of use
The vials should be shaken before use.

Propofol 20 mg/ml does not contain any antimicrobial preservation media, and the growth of microorganisms is facilitated due to its composition. Therefore, the emulsion must be used ***immediately***.

Strict asepsis must be adhered to both for Propofol 20 mg/ml and for the infusion equipment used during the period of infusion. The addition of drugs or fluids into the ongoing infusion of Propofol 20 mg/ml must occur in close proximity to the cannula.

When using Propofol 20 mg/ml, no bacteria filters may be used.

The duration of an infusion of Propofol 20 mg/ml from **one** infusion system may not exceed 12 hours, as is customary for fat emulsions. At the end of the infusion, but after 12 hours at the latest, residual quantities of Propofol 20 mg/ml and the infusion system may not be further used; if necessary, the infusion system must be changed out.

Propofol 20 mg/ml must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol together with glucose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or sodium chloride 1.8 mg/ml (0.18%) and glucose 40 mg/ml (4%) solution for injection and preservative-free lidocaine 10 mg/ml (1 %) solution for injection via a Y-connector close to the injection site is possible.

Propofol 20 mg/ml
To reduce pain at the injection site, Propofol 20 mg/ml should be administered in a larger vein or lidocaine injection solution may be administered before induction of anaesthesia with Propofol 20 mg/ml.

The muscle relaxants atracurium and mivacurium should not be administered through the same intravenous access as Propofol 20 mg/ml without first rinsing it out.
The content of a vial and the respective infusion system are only intended for a ***single*** use in ***one*** patient.

Duration of use
Propofol 20 mg/ml may only be used in a patient for a maximum of 7 days.

4.3 Contraindications

Do not use Propofol 20 mg/ml:

- in the case of hypersensitivity to the active substance, soybeans, peanuts, or to any of the other ingredients of the emulsion listed in section 6.1,
- as anaesthesia in children under 3 years of age,
- for the sedation of patients aged 16 years or younger as part of intensive care (see section 4.4).

4.4 Special warnings and precautions for use

During the use of Propofol 20 mg/ml for sedation for surgical and diagnostic procedures, the patient must be continually monitored for the first signs of a decrease in blood pressure, respiratory tract obstruction and oxygen deficiency.

As is also the case with other sedatives, spontaneous movements of the patient during surgical procedures may occur with the use of Propofol 20 mg/ml for sedation. For procedures that require an immobile patient, these movements may jeopardise the success of the operation.

Misuse and dependency on Propofol has been reported, primarily among healthcare personnel. As with all medications for general anaesthesia, it may not be used without securing an airway; otherwise, there is the risk of deadly respiratory complications.

After the use of Propofol 20 mg/ml, it should be ensured that the patient has fully recovered from the anaesthesia prior to discharge.

In individual cases, a postoperative unconsciousness phase can occur with the use of Propofol 20 mg/ml, which may be accompanied by increased muscle tone. The occurrence of this is dependent on whether or not the patient was previously awake. Even though the patient will spontaneously regain consciousness, an unconscious patient should be kept under intensive observation.

The impairments caused by Propofol 20 mg/ml are usually not observed for longer than 12 hours.
When explaining the effect of Propofol 20 mg/ml to the patient, and when making the following recommendations, the doctor should take into consideration the type of procedure, the concomitant medication, the age and the condition of the patient.

- The patient should only return home when accompanied by another person.
- The patient should be made aware of when manual activities or activities requiring dexterity / risky activities (e.g. operating a motor vehicle) can be carried out again.

- The patient should be made aware that taking other sedatives (e.g. benzodiazepine, opiates, alcohol) may prolong and increase the impairments.

As with other intravenous anaesthetics, Propofol 20 mg/ml should be administered in a slower manner than usual and used with particular caution in patients with cardiac, respiratory, renal and hepatic disorders, hypovolemia or who are in a reduced general state of health (see section 4.2).

Heart, circulatory and respiratory insufficiency as well as hypovolaemia should be compensated prior to administration of the drug, if possible.

In the case of patients with severe cardiac damage, Propofol 20 mg/ml must be administered with corresponding caution and in combination with intensive monitoring.

A pronounced drop in blood pressure may necessitate the administration of plasma substitutes, possibly of vasoconstrictors, and slower administration of Propofol 20 mg/ml. The possibility of a massive drop in blood pressure should be taken into consideration for patients with reduced coronary or cerebral perfusion or with hypovolemia.

The Propofol clearance is dependent on the blood flow. Therefore, if drugs are used at the same time that reduce the cardiac output, the Propofol clearance will also be reduced.

Propofol does not have a vagolytic effect. The use has been associated with the occurrence of bradycardia with an occasionally severe outcome (cardiac arrest). Therefore, in situations where there is pre-existing high vagal tone or Propofol 20 mg/ml is administered with other drugs, which may decrease the heart rate, intravenous administration of an anticholinergic agent should be considered before or during anaesthesia with Propofol 20 mg/ml.

When using Propofol 20 mg/ml in people with epilepsy, it is possible for a seizure to be triggered.

Before repeated or longer (> 3 hours) use of Propofol in small children (< 3 years of age) and pregnant women, the benefits and risks of the planned procedure should be taken into account, since there are reports of neurotoxicity from preclinical studies; see section 5.3.

Paediatric Population
The use of Propofol 20 mg/ml in newborns is not recommended, since this patient group has not been sufficiently evaluated.

Pharmacokinetic data (see section 5.2) indicate that the clearance of Propofol is considerably reduced in newborns and varies widely per individual. When using doses that are recommended for older children, an overdose could occur and lead to severe circulatory and respiratory depression (see section 4.8).

Propofol 20 mg/ml is not recommended for children under 3 years of age, since a corresponding titration of Propofol 20 mg/ml for small children can only be carried out with difficulty on account of the extraordinarily small volume required.

Propofol may not be used for sedation in patients 16 years of age or younger during intensive care, since the safety and efficacy of Propofol has not been validated for sedation in this age group (see section 4.3).

Notes regarding intensive medical care
The use of infusions with Propofol emulsion for sedation as part of intensive care is associated with a series of metabolic disorders and organ failure, which may lead to death.

In addition, combined occurrence of the following undesirable effects has also been reported: metabolic acidosis, rhabdomyolysis, hyperkalaemia hepatomegaly, renal failure, hyperlipidaemia, heart arrhythmia, Brugada-type ECG (saddle or tent shaped ST segment elevations in the right precordial leads [V1-V3] and concave T waves) and/or quickly progressing heart failure, which was usually not able to be treated with supportive inotropic therapeutic measures.

The combination of these events is also called "Propofol infusion syndrome".

These events were most frequently observed in patients with severe head injuries and in children with respiratory tract infections, which had received higher doses than is foreseen for adults for the purpose of sedation during intensive care.

The following factors are believed to be significant risk factors for the development of this complication:
Low oxygen saturation in tissue, severe neurological damage and/or sepsis; high doses of one or more of the following listed drugs: vasoconstrictors, steroids, inotropic agents and/or Propofol (usually at dosages of > 4 mg Propofol/kg of body mass per hour for more than 48 hours).

The prescribing doctor should be aware of these possible undesired effects in patients with the risk factors described above and immediately discontinuethe use ofpropofol if signs of the symptoms described above occur. All sedatives and drugs, which are used during intensive care, should be titrated in such a way that optimal oxygen supply is ensured and the haemodynamic parameters remain optimised. In the case of these changes in therapy, patients with elevated intracranial pressure should receive an appropriate treatment that supports cerebral perfusion. The treating doctor should make sure that the recommended dosage of 4 mg Propofol/kg of body mass per hour is not exceeded, to the greatest extent possible. Attention must be paid to lipid metabolism disorders or other disorders, as a result of which fat-containing emulsions should be used with caution.

A check of the lipid metabolism parameters is recommended if Propofol 20 mg/ml is used in patients, where there is the suspicion of elevated blood lipid values. The administration of Propofol 20 mg/ml should be adjusted accordingly if the analysis indicates a lipid metabolism disorder. In the case of patients that are simultaneously receiving parenteral nutrition, the quantity of lipids administered as a result of Propofol 20 mg/ml should be taken into account. 1.0 ml Propofol 20 mg/ml contains 0.1 g of fat.

Additional precautions
Patients with mitochondrial disorders should be treated with caution. These patients could experience an exacerbation of their disease if anaesthesia is used on them or a surgical procedure or intensive care treatment is administered. It is recommended that a normal body temperature be maintained for these patients, that carbohydrates by administered and that they be

provided with sufficient fluids. The early signs of an exacerbation of a mitochondrial disorder and Propofol infusion syndrome may be similar.

Propofol 20 mg/ml does not contain any antimicrobial preservation media, and the growth of microorganisms is facilitated due to its composition.

If Propofol 20 mg/ml is administered in combination with lidocaine, it should be noted that lidocaine may not be administered to patients with hereditary acute porphyria.

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

4.5 Interaction with other medicinal products and other forms of interaction

Propofol 20 mg/ml is compatible with other agents used for anaesthesia (premedication, muscle relaxants, inhaled , anaesthesia, analgesics, local anaesthetics). In the case of regional anaesthesia procedures, smaller doses of Propofol 20 mg/ml may be necessary. No indications of severe interactions have been observed. Some of the agents mentioned may decrease the blood pressure or impair respiration so that there can be cumulative effectswith the use of Propofol 20 mg/ml. A pronounced decrease in blood pressure when inducing anaesthesia with Propofol has been reported in patients that were treated with rifampicin.

If opiates are additionally administered prior to the anaesthesia, apnoea can occur more frequently and for a longer period of time.

In patients that take valproate, the necessity of lower doses of Propofol has been observed. In the case of simultaneous use, a reduction in the propofol dose may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of propofol 20 mg/ml during pregnancy has not been proven. Therefore, propofol 20 mg/ml should only be used during pregnancy if absolutely necessary.
Propofol 20 mg/ml crosses the placenta and may be associated with the depression of vital functions in newborns (see also section 5.3). Propofol can be employed as anaesthesia in the case of termination of pregnancy.

High dosages (more than 2.5 mg Propofol/kg of body mass for induction or 6 mg Propofol/kg of body mass per hour for maintenance of anaesthesia) should be avoided.

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

Breast-feedingStudies with breast-feeding women have shown that propofol passes into breast milk in small quantities. Therefore, mothers should suspend breast-feeding for up to 24 hours after administration of Propofol and discard the corresponding breast milk.

4.7 Effects on ability to drive and use machines

After the administration of Propofol 20 mg/ml, the patient should be observed for an appropriate period of time. Patients should be made aware of fact that the ability to participate in traffic and use machinery may be impaired for some time after the administration of Propofol 20 mg/ml. The impairments caused by Propofol 20 mg/ml are usually not observed for longer than 12 hours (see section 4.4) The patient may only return homewhen , accompanied by another person and may not drink any alcohol.

4.8 Undesirable effects

The induction and maintenance of anaesthesia and sedation with Propofol is normally gentle with only a few signs of excitation. The most frequently reported undesirable effects are pharmacologically foreseeable effects of anaesthetics / sedatives, such as, for example, hypotension and respiratory depression. The type, severity and frequency of these effects which were observed in patients during the use of Propofol, are dependent on the patient's state of health, the type of procedure and the therapeutic measures taken. The indication of the frequency of undesirable effects is based on the following categories:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000);
not known (the frequency cannot be assessed on the basis of the available data).

The following undesirable effects were particularly observed:

System Organ Classes	**Indications of Frequency**	**Undesirable effects**
Immune system disorders	Very rare	severe allergic reactions (anaphylaxis), which can include angiooedema, bronchospasm, erythemas and hypotension
Metabolism and nutrition disorders	Not known	Metabolic acidosis[5], hyperkalaemia[5], hyperlipidaemia[5]
Psychiatric disorders	Not known	euphoric mood during the waking phase, abuse of the drug and dependency on the drug[8]
Nervous system disorders	Common	Spontaneous movements and muscle spasms during the
		induction of anaesthesia, headache during the waking phase
	Rare	Feeling of dizziness, chills and perception of cold during the waking phase, episodes similar to epilepsy with seizures and opisthotonus during induction, maintenance and the waking phase (very rarely delayed by hours to a few days)
	Very rare	postoperative unconsciousness (also see section 4.4)
	Not known	Involuntary movements
Cardiac disorders	Common	Bradycardia[1]
	Very rare	Pulmonary oedema
	Not known	Arrhythmia[5], heart failure [5,7]
Vascular disorders	Common	Hypotension[2]
	Uncommon	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Common	Hyperventilation and coughing during induction of anaesthesia, temporary apnoea during induction of anaesthesia
	Uncommon	Coughing during maintenance therapy
	Rare	Coughing during the waking phase
	Not known	Respiratory depression (depending on the dosage)
Gastrointestinal tract disorders	Common	Singultation during the induction, nausea and vomiting during the waking phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known	Hepatomegaly[5]
		Hepatitis, acute hepatic failure[10]
Musculoskeletal and connective tissue disorders	Not known	Rhabdomyolysis [3,5]
Renal and urinary disorders	Very rare	Discolouration of urine after longer periods of administration of Propofol 20 mg/ml
	Not known	Renal failure[5]
Reproductive tract and breast disorders	Very rare	Sexual disinhibition
	Not known	Priapism

General disorders and administration site conditions	Very common	Local pain during the first injection[4]
	Common	Hot flushes during the induction of anaesthesia
	Very rare	Severe tissue reactions and tissue necrosis[9] after erroneous extravascular application
	Not known	Local pain, swelling following erroneous extravascular application
Investigations	Not known	Brugada-type ECG[5,6]
Injury, poisoning and complications as a result of a procedure	Very rare	Postoperative fever

After simultaneous administration of lidocaine, the following side effects can occur: dizziness, vomiting, drowsiness, convulsions, bradycardia, arrhythmia and shock.

Soybean oil may trigger allergic reactions very rarely.

1. Severe bradycardia is rare; in some individual cases, progression up to and including asystole has been reported.
2. Occasionally, a decrease in blood pressure can make volume replacement therapy and a decrease in the speed of administering Propofol 20 mg/ml necessary.
3. Rhabdomyolysis was reported very rarely if Propofol 20 mg/ml was administered in high doses as 4 mg Propofol/kg of body mass per hour for sedation as part of intensive care.
4. This can be avoided for the most part by administering lidocaine simultaneously and by administering the drug in larger veins in the forearm or the cubital fossa.
5. A combination of these events, which is also called "Propofol infusion syndrome", occurs in severely ill patients who often have multiple risk factors for the development of these events (also see section 4.4).
6. Brugada syndrome - elevated ST segment and concave T waves in the ECG.
7. Quickly progressing heart failure (in some cases with a deadly outcome) in adults, which was usually not able to be treated with supportive inotropic therapeutic measures.
8. Misuse and dependency on Propofol, primarily by healthcare personnel.
9. In cases where viability of the tissue was impaired, necrosis has been reported.
10. After both long-and short-term treatment and in patients without underlying risk factors.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 (see details below).

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

An overdose can lead to circulatory and respiratory depression. Apnoea requires artificial ventilation. In the case of circulatory depression, the usual measures should be taken of lowering the head position and/or plasma substitution and vasoconstrictors.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Other general anaesthetics,
ATC-code N0lAXl0.

After intravenous injection of Propofol 20 mg/ml, a hypnotic effect occurs quickly. The induction time is dependent on the injection speed and is normally 30 -40 seconds. The duration of effect is short as a result of rapid metabolisation and excretion (4-6 minutes). The mechanism of action is not completely known, as with all general anaesthetics. However, it is believed that Propofol produces its sedative or anaesthetic effect by means of positive modulation of the inhibitory effect of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors.

When the dosing guidelines are followed, a clinically relevant accumulation of propofol after multiple repeated injections or infusion can be ruled out. Most patients awake quickly in a clearly conscious state.

Limited studies on the duration of action of anaesthesia with propofol in children indicate that the safety and efficacy remain unchanged up to a duration of action of 4 hours.
References in literature regarding the use of Propofol in children also indicate that there are no changes with respect to the safety and efficacy when Propofol is used with longer treatments .

The occasionally observed bradycardia and drop in blood pressure when inducing anaesthesia are most likely attributed to a central vagotonic effect or to an inhibition of the activity of the sympathetic nervous system. The circulatory situation generally normalises when continuing the anaesthesia.

5.2 Pharmacokinetic properties

Propofol is up to 98 % bound to plasma protein.

After intravenous administration, the initial progression of the blood concentration (alpha phase) is characterised by a large decrease due to the rapid distribution inthe organism .The half-life of the alpha phase is 1.8 - 4.1 minutes.
The decrease in the blood concentration is slower during the elimination or beta phase. The half-life for this phase was calculated at 34 to 64 minutes. A so-called deep compartment can be identified over a longer period of observation. The half-life for this phase (gamma phase) of the blood concentration is 184 - 382 minutes.

The initial distribution volume V amounts to 22 - 76 l, and the total distribution volume $Vd_{ß}$ is
387 - 1,587l.

Propofol has a large distribution volume and is quickly eliminated from the body (total clearance: 1.5 - 2 l/min). The elimination occurs through metabolisation, primarily in the liver, where inactive conjugates of Propofol and the corresponding hydroquinone are formed depending on the blood flow, which undergo renal excretion.

After a single intravenous dose of 3 mg Propofol/kg, the Propofol clearance per kg of body weight increased depending on the patient's age in the following manner: the mean clearance in newborns < 1 month of age (n=25), at 20 ml/kg/min was considerably lower in comparison to older children (n=36, aged 4 months to 7 years). In the case of newborns, the data additionally exhibit considerable variability (3.7 - 78 ml/kg/min). Due to these limited study results, which indicate a large degree of variability, no dosage recommendation can be provided for this age class.

In the case of older children, the mean clearance of Propofol after a single bolus administration of 3 mg Propofol/kg was 37.5 ml/kg/min in children in the age of 4 - 24 months (n=8), 38.7 ml/kg/min in children in the age of 11 - 43 months (n=6), 48 ml/kg/min in children in the age of 1 - 3 years (n=12) and 28.2 ml/kg/min in children in the age of 4 - 7 years (n=10). In comparison, the mean clearance in adults was 23.6 ml/kg/min (n=6).

Propofol is predominantly metabolised in the liver. Glucuronides of the propofol and glucuronides as well as sulphate conjugates of2.6-diisopropyl-1.4-quinol are found as metabolites. 40% of the administered dose is present in the form of glucuronide of Propofol. All metabolites are inactive. Approximately 88 % of the applied Propofol is excreted in the urine in the form of metabolites and approx. 0.3 % is unchanged in the stool.

Bioavailability:
Intravenous administration: 100%

5.3 Preclinical safety data

Acute toxicity

The intravenous LD_{50} in mice is 53, and in rats it is 42 mg Propofol/kg of body weight.

Chronic toxicity
Chronic toxicity trials have been carried out on rats and dogs. Doses of 10 - 30 mg Propofol/kg of body mass were administered daily or 2-3 x per week for up to one month as an infusion. There were no indications of toxic effects or pathological changes.

Mutagenic effect
In-vitro studies in Salmonella thyphimurium (Ames test) and Saccharomyces cerevisiae as well as in-vivo studies in mice and Chinese hamsters did not show any indications of a mutagenic effect.

Reproduction toxicity
Propofol 20 mg/ml crosses the placenta. Embryo toxicity studies in rats and rabbits did not provide any indication of a teratogenic effect.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrates that the use of anaesthetics 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 in not known.

Propofol 20 mg/ml passes into breast milk. There is no experience in humans with use during pregnancy and the lactation period.

Carcinogenicity
Long-term studies regarding the potential for causing tumours have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
Medium-chain triglycerides
Glycerol
Egg lecithin
Sodium oleate
Sodium Hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Propofol 20 mg/ml must not be mixed with other solutions for injection or infusion.
For further details see section 6.6.

The muscle relaxants Atracurium and Mivacurium should not be administered through the same intravenous access as Propofol 20 mg/ml without first rinsing it out (also see section 4.2).

6.3 Shelf life

2 years.
After first opening: to be used immediately.
Chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.

6.4 Special precautions for storage

Store below 25° C.
Do not freeze.

6.5 Nature and contents of container

Colourless glass vial (type II) of 50 ml with a grey bromobutyl rubber closure and aluminium cap fitted with plastic flip-off disc, packs of 1 and 10 unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Containers should be shaken before use.

Propofol 20 mg/ml must not be mixed with other solutions for injection or infusion. However, co-administration of Propofol together with glucose 50 mg/ml (5%) solution for injection, sodium chloride 9 mg/ml (0.9%) solution for injection or sodium chloride 1.8 mg/ml (0.18%) and glucose 40 mg/ml (4%) solution for injection and preservative-free lidocaine 10 mg/ml (1 %) solution for injection via a Y-connector close to the injection site is possible.

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

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/038/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 August 2011
Date of last renewal: 28 April 2016

10 DATE OF REVISION OF THE TEXT

September 2024