IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0740/010/003
Case No: 2061162

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Genthon B.V.

Microweg 22, **Nijmegen 6545 CM**, **Netherlands**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Propofol 20 mg/ml, emulsion for injection and infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/02/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Propofol 20 mg/ml, emulsion for injection and infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 20 mg propofol.
One 20 ml ampoule contains 400 mg propofol.
One 50 ml vial contains 1000 mg propofol.
One 100 ml vial contains 2000 mg propofol.

Excipient: one ml contains 100 mg refined soya-bean oil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection and infusion.
Isotonic, white oil-in-water emulsion for intravenous administration

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Propofol 20 mg/ml is indicated:
- for induction and maintenance of general anaesthesia.
- for sedation of artificially ventilated patients in the Intensive Care Unit.

4.2 Posology and method of administration

The dose of Propofol 20 mg/ml should be individualised by an experienced anaesthetist based on body weight, sensitiveness of the patient and other concomitant medications. Propofol is a short-acting intravenous anaesthetic agent and it has been used in association with spinal and epidural anaesthesia.

It is recommended that propofol should be titrated against the response of the patient until clinical signs show the onset of anaesthesia.

The contents of one ampoule or one vial of Propofol 20 mg/ml are for single use in one patient.

Induction of general anaesthesia:
Adults:
The dose for adults aged less than 55 years is 1.5 - 2.5 mg/kg body weight.
Healthy adults require an administration rate of approximately 1-2 ml (20-40 mg) per 10 seconds. For patients at increased risk (ASA grades III and IV) the administration rate is 1 ml (20 mg) per 10 seconds.

Children:
Propofol 20 mg/ml is not advised for induction of general anaesthesia in children younger than 1 month of age.
It is recommended to administer Propofol 20 mg/ml slowly and against the response until clinical signs show the onset of anaesthesia.

The dose should be adjusted for age and body weight.

Children over 8 years of age require approximately 2.5 mg/kg. Below this age, the dose requirement may be higher (2.5-4 mg/kg). Due to the lack of clinical experience, lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Elderly:
Patients over 55 years of age require generally a lower dose.

Maintenance:
Anaesthesia should be maintained by administering Propofol 20 mg/ml by continuous infusion to prevent the clinical signs of light anaesthesia.
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Adults via infusion: 4 - 12 mg/kg/h.
Elderly, weak patients, hypovolaemic patients and patients with ASA grades III and IV via infusion: 4 mg/kg/h.
Children via infusion: 9 - 15 mg/kg/h.

Propofol 20 mg/ml is not advised for maintenance of general anaesthesia in children younger than 1 month of age.
Sedation in the Intensive Care Unit:
For sedation with Propofol 20 mg/ml in the Intensive Care Unit, a continuous infusion should be used. The rate of administration is dependent on the desired level of sedation. Generally satisfactory sedation will be obtained with a dose of 0.3 - 4.0 mg/kg/h.

Prescribers are reminded the dosage of 4 mg/kg/h should not be exceeded if possible (see 4.4 Special warnings and precautions for use).

Propofol is not indicated for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications).

Administration of propofol by volumetric infusion pump is not advised for sedation in the intensive care unit.

Administration via infusion:
Propofol 20 mg/ml should not be administered as bolus injection but only as infusion.
Propofol 20 mg/ml may be administered by a variety of infusion control techniques.
For administration of the Propofol 20 mg/ml for maintenance of anaesthesia the use of a volumetric infusion pump or a syringe pump is recommend to control the administration rate.
Propofol 20 mg/ml should not be diluted.
Propofol 20 mg/ml should not be mixed prior to administration with injections or infusion fluids. However, Propofol 20 mg/ml may be co-administered via a Y-piece connector close to the injection site with the following:
- Dextrose 5 %.
- Sodium Chloride 0.9 %.

Duration of administration:
The duration of administration should not exceed 7 days.

4.3 Contraindications

Hypersensitivity to propofol or to one of the excipients.

Propofol contains soyabean oil. Therefore it should not be used in patients who are allergic to peanuts or soya.

Propofol is contraindicated for sedation in intensive care of patients of 16 years of age or younger (see 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Propofol 20 mg/ml should be administered only by a physician capable in the field of anaesthesia and/or intensive care and facilities for resuscitation should be available immediately.

During the administration of propofol, patients should be monitored continuously to observe possible hypotension, obstruction in the respiratory tract or insufficient oxygen intake.

In elderly or debilitated patients, patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic patients propofol should be administered with caution and reduced dose, see section 4.2.
When propofol is administered to epileptic patients there may be an increased risk of convulsions.

Because of the haemodynamic effects on the cardiovascular system propofol should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and reduced dosage and with intensive cardiovascular monitoring.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia, occasionally profound, and asystole. The intravenous administration of an anticholinergic agent before induction or during maintenance of anaesthesia should be considered especially where vagal tone is likely to predominate or when propofol is used in conjunction with other agents likely to cause bradycardia.

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

Use of Propofol 20 mg/ml is not recommended with electroconvulsive therapy**.**

Propofol contains egg lecithin as emulsifier. Following dissolution, lysolecithin is formed, a compound with haemolytic properties in vitro. In the clinical situation, even when dissolution is complete, risk of haemolysis will be low when the recommended dosage is applied. Under pathological conditions (patients with hepatic- and/or renal failure) in case of low albumin concentration this risk increases and should be checked for on a regular basis.

Soya-bean oil may rarely cause allergic reactions.

Full recovery from general anaesthesia should be confirmed prior to discharge.

Because Propofol 20 mg/ml is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of micro-organisms, the administration systems with undiluted Propofol 20 mg/ml should be replaced 12 hours after opening of the ampoule or vial.
Propofol 20 mg/ml should not be administered via a microbiological filter.

Special care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used with caution.
Lipids should be monitored in ICU treatment after 3 days.
When the patient is receiving via infusion both Propofol 20 mg/ml and intravenous lipids, the amount of lipids should be reduced because Propofol 20 mg/ml also contains lipids (0.1 gram fat per 1 ml emulsion).

In individual cases postoperative unconsciousness with increased muscle tone has been reported after administration of propofol. The unconsciousness is independent of the fact whether the patient has been awake already or not. Although the patient's recovery occurs spontaneously the unconscious patient has to be monitored intensively.

Co-administration of other drugs or other fluids added to an infusion line with Propofol 20 mg/ml must occur close to the cannula site.

Local pain at the injection site can be reduced by administration into a large vein in the lower arm or the antecubital fossa. In order to reduce pain on initial injection, lidocaine may be given prior to injection of propofol.

Serious adverse events including deaths, have been reported in connection with the improper use of propofol, i.e. sedation of children (mainly those with airway infections) where higher doses are applied than recommended for adults. However, no causal relationship to propofol has been established.

Propofol is not advised for general anaesthesia in children younger than 1 month of age. The safety and efficacy of propofol (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/pr rapidly progressive cardiac failure (in some cases with fatal outcome) in adults treated for more than 58 hours with dosages in excess of 5 mg/kg/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the intensive care unit. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
Prescribers are reminded if possible the dosage of 4 mg/kg/h should not be exceeded. Dosages of 4 mg/kg/h are usually sufficient for sedation of mechanically ventilated patients in the intensive care unit (ICU) situation (treatment durations in excess of 1 day). Dosages above 4 mg/kg/h have been associated with an increased risk of developing a syndrome characterised by rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, which can be fatal. Prescribers should be alert to these possible undesirable effects and decrease the dosage or switch to an alternative sedative at the first sign of occurrence of symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

It should be taken into consideration that concomitant use of propofol and premedication, inhalational agents, analgesic agents, muscle relaxants or local anaesthetics may potentiate anaesthesia and cardiovascular side effects.
After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea. Adjustment of the maintenance dose is not necessary.

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

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Leucoencephalopathy has been reported with administration of lipid containing emulsions such as propofol in patients receiving cyclosporine.

4.6 Pregnancy and lactation

The safety of propofol during pregnancy has not been established. Therefore propofol should not be used in pregnant women unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression (see also 5.3 reproductive toxicity). High doses (more than 2.5 mg/kg for induction or 6 mg/kg/h for maintenance of anaesthesia) should be avoided.

Studies in breast-feeding women showed that propofol is excreted in small amounts into the milk. Therefore, mothers should stop breast-feeding and discard breast milk for 24 hours after administration of propofol.

4.7 Effects on ability to drive and use machines

The patient should be advised that driving a vehicle or operating a machine might be impaired for some time after general anaesthesia.

4.8 Undesirable effects

Induction of anaesthesia is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic agent, such as hypotension. Given the nature of anaesthesia and those patients receiving intensive care, events reported in association with anaesthesia and intensive care may also be related to the procedures being undertaken or the recipient's condition.

Very common (≥1/10)	*General disorders and administration site conditions:*	Local pain on induction [1]
Common (≥1/100, <1/10)	*Vascular disorder:*	Hypotension [2]
	Cardiac disorders:	Bradycardia [3]
	Respiratory, thoracic and mediastinal disorders:	Transient apnoea during induction
	Gastrointestinal disorders:	Nausea and vomiting during recovery phase
	Nervous system disorders:	Headache during recovery phase
	General disorders and administration site conditions:	Withdrawal symptoms in children [4]
	Vascular disorders:	Flushing in children [4]
Uncommon (≥1/1000, <1/100)	*Vascular disorders:*	Thrombosis and phlebitis
Rare (≥1/10 000, <1/1000)	*Nervous system disorders:*	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
Very rare (<1/10 000)	*Musculoskeletal and connective tissue disorders:*	Rhabdomyolysis [5]
	Gastrointestinal disorders:	Pancreatitis
	Injury, poisoning and procedural complications:	Post-operative fever
	Renal and urinary disorders:	Discolouration of urine following prolonged administration
	Immune system disorders:	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
	Reproductive system and breast disorders:	Sexual disinhibition
	Cardiac disorders:	Pulmonary oedema

Nervous system disorders:	Postoperative unconsciousness

(1) May be minimised by using the larger veins of the forearm and antecubital fossa. With Propfol local pain can also be minimised by the co-administration of lidocaine.
(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of Propofol.
(3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
(4) Following abrupt discontinuation of Propofol during intensive care.
(5) Very rare reports of rhadbomyolysis have been received where Propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
Pulmonary oedema, hypotension, asystole, bradycardia, and convulsions, have been reported. In very rare cases rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, sometimes with fatal outcome, have been observed when propofol was administered at dosages in excess of 4 mg/kg/h for sedation in the intensive care unit (see 4.4 Special warnings and precautions for use). Dystonia/dyskinesia have been reported.
Reports from off-label use of Propofol for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied.

4.9 Overdose

Overdosage may cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression requires lowering the patient's head (Trendelenburg-position), and in severe cases the use of plasma expanders and pressor agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics
ATC code: N01AX10

Propofol is a short-acting intravenous anaesthetic agent for induction and maintenance of general anaesthesia and for sedation of patients in the Intensive Care Unit. Propofol has a rapid onset of action and the duration of anaesthesia, depending on the dose and co-medication, is 10 minutes to 1 hour. The patient's recovery is fast and clear-headed. Opening of the eyes is possible within 10 minutes. The mechanism of action of propofol is not clear yet. There are no specific receptor sites identified. It is generally accepted that anaesthetic agents cause a non-specific effect at the level of the lipid membranes.

5.2 Pharmacokinetic properties

Propofol is 97% bound to plasma proteins. After intravenous infusion an elimination half-life between 277 and 403 minutes was found. Following intravenous bolus administration the kinetics of propofol can be described by a three compartment model: A fast distribution phase ($t_{1/2}$=1.8 to 4.1 minutes), a β-elimination phase ($t_{1/2}$=30 to 60 minutes) and a γ-elimination phase ($t_{1/2}$=200 to 300 minutes). In the γ-elimination phase the decrease in blood levels is slow because of the slow redistribution from a deep compartment, probably fat tissue. This phase does not affect the recovery time in clinical practice.
Propofol is mainly metabolised by conjugation in the liver with a clearance of about 2 l/min but there is also extrahepatic metabolism. The inactive metabolites are excreted mainly by the kidney (approximately 88 %). Under the usual maintenance regimen, significant accumulation of propofol has not been seen after surgical procedures of at least 5 hours.

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.
Reproductive toxicity studies have shown effects related to pharmacodynamic properties of propofol only at high doses. Teratogenic effects have not been observed.
Paravenous, subcutaneous and intramuscular injection resulted in mild to moderate local intolerance around the injection site.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol, egg-lecithin, refined soya-bean oil, oleic acid, sodium hydroxide and water for injections.

6.2 Incompatibilities

The neuromuscular blocking agents atracurium and mivacurium should not be given through the same intravenous line as Propofol 20 mg/ml without prior flushing.

Propofol 20 mg/ml should not be mixed prior to administration with injections or infusion fluids. However, Propofol 20 mg/ml may be administered via a Y-piece connector close to the injection site with the products mentioned in section 4.2.

6.3 Shelf Life

3 years.

Any portion of the contents remaining after first use should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Do not freeze.

6.5 Nature and contents of container

Glass ampoules of 20 ml containing 400 mg propofol, packaged per 1, 5 or 10 pieces.
Glass vials of 50 ml containing 1,000 mg propofol, packaged per 1, 5 or 10 pieces.
Glass vials of 100 ml containing 2,000 mg propofol, packaged per 1, 5 or 10 pieces.
The ampoules (colourless glass Type I) and vials (colourless glass Type II) are packaged in carton boxes together with a patient information leaflet.

6.6 Special precautions for disposal and other handling

For single use only.
Finger protection should be used when ampoules are opened.
In order to eliminate the risk of infection from bacterial contamination strict aseptic techniques must be used when handling propofol emulsion.
Please inspect the product visually before using.
Shake before use.
When two layers can be seen in the ampoule or vial after shaking then the product should not be used.
If other visual appearances have changed or if the container is damaged the product should not be used.
Propofol 20 mg/ml should not be diluted.
Any portion of the contents remaining after first use should be discarded.

7 MARKETING AUTHORISATION HOLDER

Genthon BV
Microweg 22
Nijmegan 6545 CM
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 740/10/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th October 2000

Date of last renewal: 23rd November 2007

10 DATE OF REVISION OF THE TEXT

January 2009