SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Propofol BioQ Pharma 10 mg/ml (1%) emulsion for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion for injection/infusion contains 10 mg propofol.

Each 20 ml ampoule/vial contains 200 mg propofol.

Each 50 ml vial contains 500 mg propofol.

Each 100 ml vial contains 1,000 mg propofol.

Excipient with known effect

1 ml emulsion for injection/infusion contains 100 mg soya-bean oil, refined.

Each 20 ml ampoule/vial contains 2 g soya-bean oil, refined.

Each 50 ml vial contains 5 g soya-bean oil, refined.

Each 100 ml vial contains 10 g soya-bean oil, refined.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection/infusion.

White aqueous isotonic oil-in-water emulsion.

Osmolarity: 285 to 320 mOsm/Kg.

pH is in the range of 6.0 – 8.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Propofol BioQ Pharma 10 mg/ml is a short-acting intravenous general anaesthetic for:

- Induction and maintenance of general anaesthesia in adults and paediatric patients > 1 month of age

- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and paediatric patients > 1 month of age
- Sedation of ventilated patients > 16 years of age in the intensive care unit

4.2 Posology and method of administration

Propofol BioQ Pharma 10 mg/ml must only be administered 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 oximetry) and facilities for maintenance of a patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.

For sedation during surgical and diagnostic procedures Propofol BioQ Pharma 10 mg/ml should not be administered by the same person conducting the surgical or diagnostic procedure.

Propofol BioQ Pharma 10 mg/ml has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to Propofol BioQ Pharma 10 mg/ml.

Posology

The dose of Propofol BioQ Pharma 10 mg/ml should be individually adapted according to the patient's response.

Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

General anaesthesia in adults

Induction of anaesthesia

For induction of anaesthesia Propofol BioQ Pharma 10 mg/ml must be titrated (20-40 mg propofol every 10 seconds) against the response of the patient until clinical signs show the onset of anaesthesia.

Usually an adult patient below 55 years will require 1.5 to 2.5 mg propofol/kg body weight.

In patients over 55 years and in patients of ASA (American Society of Anaesthesiologists) classification III and IV, especially in those with impaired cardiac function, the requirements will generally be less and the total dose of Propofol BioQ Pharma 10 mg/ml may be reduced to a minimum of 1 mg propofol/kg body weight.

These patients also need lower rates of administration (approximately 2 ml corresponding to 20 mg propofol every 10 seconds).

Maintenance of anaesthesia

Anaesthesia can be maintained by administering Propofol BioQ Pharma 10 mg/ml either by continuous infusion or repeat bolus injections (Propofol BioQ Pharma 10 mg/ml only).

Continuous infusion

When using a continuous infusion for maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg body weight/hr should be given. 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 BioQ Pharma 10 mg/ml may be further reduced depending on the patient's condition and on the applied anaesthetic method.

Repeat bolus injection

For maintenance of anaesthesia using repeat bolus injections dosages of 25 mg up to 50 mg (= 2.5 up to 5 ml Propofol BioQ Pharma 10 mg/ml) should be administered depending on the clinical requirements.

Sedation of mechanically ventilated patients during intensive care

Adults and adolescents (≥ 16 years of age)

When used to provide sedation for mechanically ventilated patients under intensive care conditions, the administration of Propofol BioQ Pharma 10 mg/ml as continuous infusion is recommended. The rate of administration has to be adapted to the level of sedation required.

A satisfactory level of sedation can generally be achieved with a dosage of 0.3–4.0 mg propofol/kg body weight/hr (see section 4.4).

Administering Propofol BioQ Pharma 10 mg/ml through a TCI-system for sedation in intensive care is not recommended.

It is recommended that blood lipid levels be monitored should Propofol BioQ Pharma 10 mg/ml be administered to patients thought to be at particular risk of fat overload. Administration of Propofol BioQ Pharma 10 mg/ml 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 BioQ Pharma 10 mg/ml formulation; 1.0 ml of Propofol BioQ Pharma 10 mg/ml contains approximately 0.1 g of fat.

If the duration of sedation is in excess of 3 days, lipids should be monitored in all patients.

Sedation for diagnostic and surgical interventions in adult patients

To provide sedation during surgical and diagnostic interventions, doses and administration rates need to be adapted to the clinical response.

Most patients will require 0.5 to 1.0 mg propofol/kg body weight over 1 to 5 minutes for induction of sedation.

For maintenance of sedation the Propofol BioQ Pharma 10 mg/ml infusion should be titrated until the desired level of sedation is achieved. Generally 1.5 to 4.5 mg propofol/kg body weight/hr will be required.

The infusion may be supplemented by bolus injections of 10 to 20 mg (1 to 2 ml Propofol BioQ Pharma10 mg/ml) if a deeper level of sedation is rapidly required.

In patients older than 55 years and in patients of ASA classification III and IV the rate of administration and dosage may need to be reduced.

Paediatric population

General anaesthesia in paediatric patients (>1 month of age)

Propofol BioQ Pharma 10 mg/ml is not recommended for induction and maintenance of anaesthesia in paediatric patients less than one month of age (see section 4.4).

Induction of anaesthesia

For induction of anaesthesia Propofol BioQ Pharma 10 mg/ml should be titrated slowly until clinical signs show the onset of anaesthesia. The dose should be adjusted according to age and/or body weight. Most patients over 8 years of age require approximately 2.5 mg propofol/kg body weight for induction of anaesthesia.

In younger patients, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5-4 mg propofol/kg body weight).

Maintenance of anaesthesia

A satisfactory level of anaesthesia can generally be attained with a continuous infusion or by repeated bolus injection, using a dosage of 9 – 15 mg propofol /kg body weight/hr. The dose needs to be individually adapted and special attention needs to be given to obtain adequate analgesia.

In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher - within the recommended dosage limits.

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

Sedation of ventilated paediatric patients during intensive care

Propofol BioQ Pharma 10 mg/ml is contraindicated in paediatric patients of 16 years of age or younger in the indication for sedation in intensive care (see section 4.3).

Sedation for diagnostic and surgical interventions in paediatric patients (>1 month of age)

Doses and administration rates should be adjusted according to the required level of sedation and the clinical response. Most paediatric patients require 1 – 2 mg propofol/kg body weight for onset of sedation. Maintenance of sedation may be accomplished by titrating Propofol BioQ Pharma 10 mg/ml infusion to the desired level of sedation. Most patients require 1.5-9 mg propofol/kg body weight/hr. The infusion may be supplemented by bolus injections of up to 1 mg/kg b.w. if a deeper level of sedation is rapidly required.

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

Method of administration

Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used.

Propofol BioQ Pharma 10 mg/ml is administered intravenously as an injection or as a continuous infusion, undiluted or diluted with glucose 50 mg/ml (5%) intravenous infusion solution or sodium chloride 9 mg/ml (0.9%) intravenous infusion solution or a combination solution of glucose 40 mg/ml (4%) and sodium chloride 1.8 mg/ml (0.18%) (see section 6.6).

Prior to use, the ampoule neck and rubber stopper should be disinfected using a medicinal alcohol (spray or dipped swab). After use, any remaining contents must be discarded (see section 6.6).

Propofol BioQ Pharma 10 mg/ml does not contain antimicrobial preservatives and is capable of supporting the growth of microorganisms. The emulsion must be drawn aseptically into a sterile syringe or infusion system immediately after opening the ampoule or spiking the vial.

Administration must commence without delay. During infusion sterility of Propofol BioQ Pharma 10 mg/ml as well as the infusion system must be maintained.

Medicinal products or liquids that are added to a running Propofol BioQ Pharma 10 mg/ml infusion should be added close to the cannula.

Propofol BioQ Pharma 10 mg/ml must not be administered via infusion systems that are provided with a microbiological filter.

The contents of one vial of Propofol BioQ Pharma 10 mg/ml and any infusion equipment are intended for **single** use in **one** patient.

Any remainder must be discarded immediately after use.

Infusion of undiluted Propofol BioQ Pharma 10 mg/ml

When Propofol BioQ Pharma 10 mg/ml is administered as a continuous infusion, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

As applies to parenteral administration of all kinds of fat emulsions, the duration of use for **one** infusion system for a continuous infusion of Propofol BioQ Pharma 10 mg/ml must not exceed 12 hours. The infusion system and the container must be discarded and replaced after a maximum of 12 hours.

The simultaneous administration of Propofol BioQ Pharma 10 mg/ml together with an infusion solution of glucose 50 mg/ml (5%), sodium chloride 9 mg/ml (0.9%) intravenous infusion solution or a combination solution of glucose 40 mg/ml (4%) and sodium chloride 1.8 mg/ml (0.18%) close to the Y-connector near the place of injection, is possible.

Any Propofol BioQ Pharma 10 mg/ml remaining at the end of the infusion period or after changing the system needs to be discarded and destroyed.

Infusion of diluted Propofol BioQ Pharma 10 mg/ml

When Propofol BioQ Pharma 10 mg/ml is administered diluted as a continuous infusion it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates and to prevent the accidental administration of large volumes of diluted Propofol BioQ Pharma 10 mg/ml.

Propofol BioQ Pharma 10 mg/ml must not be mixed with other solutions for injection or infusion except those mentioned in section 6.6.

To reduce pain on the injection site lidocaine may be injected immediately before the use of Propofol BioQ Pharma 10 mg/ml or Propofol BioQ Pharma 10 mg/ml may be mixed, immediately prior to administration, with preservative-free lidocaine injection (see section 6.6). For the specific risks of lidocaine see sections 4.4 and 4.8.

The infusion system should be rinsed before administration of muscle relaxants like atracurium and mivacurium when using the same infusion system for Propofol BioQ Pharma 10 mg/ml.

<u>Duration of administration</u>

Propofol BioQ Pharma 10 mg/ml can be administered for a maximum of 7 days.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to soya or peanut.
- Sedation in the intensive care unit in paediatric patients of 16 years of age or younger (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 BioQ Pharma 10 mg/ml should not be administered by the person conducting the diagnostic or surgical procedure.

The abuse of, and dependence on propofol, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Propofol BioQ Pharma 10 mg/ml without airway care may result in fatal respiratory complications.

When Propofol BioQ Pharma 10 mg/ml 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 BioQ Pharma 10 mg/ml 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 BioQ Pharma 10 mg/ml. 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)

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedications and other agents.

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 that reduces cardiac output will also reduce propofol clearance.

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

In patients with severe cardiac impairment it is recommended that Propofol BioQ Pharma 10 mg/ml is given with great caution and under intensive monitoring.

Due to the higher doses to be usually applied in patients with severe overweight, the increased risk of adverse haemodynamic effects 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 the vagal tone is likely to predominate or when Propofol BioQ Pharma 10 mg/ml is used in conjunction with other agents likely to cause bradycardia.

Elderly

In elderly patients Propofol BioQ Pharma should be administered with caution and with a reduced administration rate (see section 4.2).

Epilepsy

When Propofol BioQ Pharma 10 mg/ml is administered to an epileptic patient, there may be a risk of convulsion.

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 a high intracranial pressure

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

Patients with hereditary disorders

Dilutions of Propofol BioQ Pharma 10 mg/ml with lidocaine solution must not be used in patients with hereditary predisposition to acute porphyria.

Paediatric population

Administration of Propofol BioQ Pharma 10 mg/ml for anaesthesia in infants and children up to the age of 3 needs extra attention, although recent data shows that there are no clear safety differences in comparison to children older than 3 years.

The use of Propofol BioQ Pharma 10 mg/ml is not recommended for newborn infants younger than 1 month as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates with a very high inter-individual variability. Relative overdose could occur administering doses recommended for older children resulting in severe cardiovascular depression.

Propofol BioQ Pharma 10 mg/ml 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).

<u>Advisory statements concerning intensive care unit management</u>

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 following extended dosing at dose rates greater than 4 mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and immediately discontinue propofol when the above signs develop. All sedative and therapeutic agents used in the intensive care unit (ICU), including propofol, 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 BioQ Pharma 10 mg/ml is administered to patients thought to be at particular risk of fat overload. Administration of Propofol BioQ Pharma 10 mg/ml 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 (e.g. parenteral nutrition) concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the Propofol BioQ Pharma 10 mg/ml formulation; 1.0 ml of Propofol BioQ Pharma 10 mg/ml 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 disorders when undergoing anaesthesia, surgery and ICU care. Maintenance or 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 BioQ Pharma 10 mg/ml contains no antimicrobial preservatives and supports growth of micro-organisms.

When Propofol BioQ Pharma 10 mg/ml is to be aspirated, it must be drawn aseptically into a sterile syringe or 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 BioQ Pharma 10 mg/ml must not be administered via a microbiological filter.

Propofol BioQ Pharma 10 mg/ml and any syringe containing Propofol BioQ Pharma 10 mg/ml are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of Propofol BioQ Pharma

10 mg/ml must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of Propofol BioQ Pharma 10 mg/ml and the infusion line must be discarded and replaced as appropriate.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Propofol BioQ Pharma 10 mg/ml 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 BioQ Pharma 10 mg/ml may be required where general anaesthesia or sedation is used as an adjunct to regional anaesthetic techniques.

Propofol hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin.

Propofol BioQ Pharma 10 mg/ml can be used in combination with other active substances for anaesthesia (premedication, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics). Until now no severe interactions with these active substances have been reported. Some of these centrally acting active substances may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Propofol BioQ Pharma 10 mg/ml.

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

When used in addition to local anaesthesia the dosage of Propofol BioQ Pharma 10 mg/ml may need to be reduced.

After additional premedication with opioids there may be a higher incidence and longer duration of apnoea.

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

It should be taken into consideration that concomitant use of propofol and active substances for premedication, volatile agents or analgesic agents may potentiate anaesthesia and cardiovascular side effects. Concomitant use of central nervous depressants e. g. alcohol, general anaesthetics, narcotic analgesics will result in intensification of their sedative effects.

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

Leukoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving ciclosporin.

A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of propofol during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Propofol BioQ Pharma 10 mg/ml should not be given to pregnant women except when absolutely necessary. Propofol crosses the placenta and can cause neonatal depression. Propofol BioQ Pharma 10 mg/ml can, however, be used during an induced abortion.

High doses (more than 2.5 mg propofol/kg body weight for induction or 6 mg propofol/kg body weight/hr for maintenance of anaesthesia) should be avoided.

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 BioQ Pharma 10 mg/ml. 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 BioQ Pharma 10 mg/ml.

After administration of Propofol BioQ Pharma 10 mg/ml 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.

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, drug abuse and drug dependence[8]
Nervous system disorders	Common (>1/100, <1/10)	Excitation, headache during recovery
	Rare (>1/10,000, <1/1,000)	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery, vertigo, shivering and sensations 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]
	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 (>1/1,000, <1/100)	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Common (>1/100, <1/10)	Transient apnoea during induction, coughing during induction
	Uncommon (>1/1,000, <1/100)	Coughing during maintenance
	Rare (>1/10,000, <1/1,000)	Coughing during recovery

System organ class	Frequency	Undesirable effects
	Frequency not known (9)	Respiratory depression (dose dependant)
Gastrointestinal disorders	Common (>1/100, <1/10)	Nausea and vomiting during recovery phase, singultus during induction
	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	Very rare (<1/10,000)	Sexual disinhibition
General disorders and administration site conditions	Very common (>1/10)	Local pain on induction[(4)]
	Common (>1/100, <1/10)	Hot flushes during induction
	Very rare (<1/10,000)	Tissue necrosis[(10)] following accidental extravascular administration
	Frequency not known[(9)]	Local pain, swelling, following 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 would 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, general; other general anaesthetics,
ATC code: N01AX10

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 - 6 minutes).

With the recommended dosage schedule a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.

Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

Paediatric population

Limited studies on the duration of propofol based anaesthesia in paediatric patients indicate safety and efficacy is unchanged up to a duration of 4 hours. Literature

evidence of use in paediatric patients documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

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

Propofol is extensively distributed (central distribution volume from 0.2 to 0.79 l/kg body weight; steady-state volume is 1.8 - 5.3 l/kg body weight) and rapidly cleared from the body (total body clearance: 1.5 - 2 l/minute). Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent to form inactive conjugates of propofol (glucoronides) and its corresponding metabolite quinol (glucoronides and sulphate compounds), which are excreted in urine (88% of the administered dose). All metabolites are inactive. Only 0.3% of the administered dose is excreted unchanged in the urine.

During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

Clearance is higher in children compared with adults.

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.

5.3 Preclinical safety data

Non-clinical 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. 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 in not known. Teratogenic effects have not been observed.

In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined

Purified egg phospholipids

Glycerol

Sodium hydroxide (for pH-adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same infusion system as Propofol BioQ Pharma 10 mg/ml without prior flushing.

6.3 Shelf life

2 years

After first opening/dilution

The mixture should be prepared aseptically immediately prior to administration and must be administered within 6 hours after preparation.

In accordance with established guidelines for other lipid emulsions, a single infusion of Propofol BioQ Pharma 10 mg/ml must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of Propofol BioQ Pharma 10 mg/ml and the infusion line must be discarded and replaced as appropriate.

Chemical and physical in-use stability of the medicinal product has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 30°C.

Do not freeze.

Keep the vial/ampoule in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml emulsion for injection/infusion in colourless Type I glass ampoules/vials with bromobutyl rubber stopper in pack sizes of 5 ampoules/vials.

50 ml emulsion for injection/infusion in colourless Type I glass vials with bromobutyl rubber stopper in the pack size of 1 vial.

100 ml emulsion for injection/infusion in colourless Type I glass vials with bromobutyl rubber stopper in the pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Propofol BioQ Pharma 10 mg/ml should not be mixed prior to administration with injection or infusion fluids other than glucose 50 mg/ml (5%) intravenous infusion solution or sodium chloride 9 mg/ml (0.9%) intravenous infusion solution or a combination solution of glucose 40 mg/ml (4%) and sodium chloride 1.8 mg/ml (0.18%).

The maximum dilution must not exceed 1 part of Propofol BioQ Pharma 10 mg/ml and 4 parts of the above mentioned intravenous infusion solution (at least 2 mg propofol/ml). The mixture should be prepared aseptically immediately prior to administration and must be administered within 6 hours after preparation.

Further Propofol BioQ Pharma 10 mg/ml may be mixed, immediately prior to administration, with preservative-free lidocaine injection (20 parts Propofol BioQ Pharma 10 mg/ml with up to one part of 1% lidocaine injection solution).

The simultaneous administration of Propofol BioQ Pharma 10 mg/ml together with an intravenous infusion solution of glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%) intravenous infusion solution or a combination solution of glucose 40 mg/ml (4%) and sodium chloride 1.8 mg/ml (0.18%) close to the Y-connector near the place of injection, is possible.

For single use only.

Parenteral products should be inspected visually for particulate matter prior to administration. If particulate matter is evident emulsion should not be used.

Containers should be shaken before use. If two layers can be seen after shaking, the emulsion should not be used.

Prior to use, the ampoule neck and rubber stopper should be disinfected using a medicinal alcohol (spray or dipped swab).

Any remaining contents after use should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45205/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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