1.3 Product Information

1.3.1 Summary of Product Characteristics

Enclosed

Summary of Product Characteristics for

Propofol Injection BP 1% w/v

1. Name of the medicinal product
Propofol Injection BP 1% w/v

2. Qualitative and quantitative composition
Each ml contains:
Propofol BP…….10mg
Water for injection BP…Q.S.

3. Pharmaceutical form
Emulsion for injection or infusion.
A milky white aqueous isotonic oil-in-water emulsion.

4. Clinical particulars

4.1 Therapeutic indications

Propofol is a short-acting intravenous anaesthetic for the
- Induction and maintenance of anaesthesia in adults and children from 1 month of age,
- sedation of ventilated patients over 16 years of age during intensive care,
- Sedation of adults or children from 1 month of age for surgical and diagnostic procedures, alone or in combination with local or regional anaesthesia.

4.2 Posology and method of administration

Propofol may only be administered by doctors that have been trained in anaesthesiology intensive care. Sedation or anaesthesia with Propofol 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.

Anaesthesia for adults:

Induction of anaesthesia:

For the induction of anaesthesia, Propofol is administered, titrated at a speed of 20 - 40 mg propofol every 10 seconds, until unconsciousness occurs.
Most adults less than 55 years of age would normallyrequire a total dose of 1.5 to 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 down to 1 mg propofol/kg body of mass, Whereby Propofol is administered at slower infusion speed (approximately 20 mg propofol every 10 seconds).

Maintenance of anaesthesia:

The anaesthesia can be maintained with a long-term infusion or repeated bolus injections of Propofol.

Continuous infusion

For maintenance of anaesthesia by means of 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 may be reduced down to 4 mg Propofol/kg of body mass per hour.

Repeated bolus injection

For maintenance of anaesthesia by means of repeated bolus injection, generally 25 - 50 mg propofol (2.5 - 5 ml Propofol 10mg/ml) are subsequently injected.

Anaesthesia in children from 1 month of age

Induction of anaesthesia

For the induction of anaesthesia, Propofol 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, especially those in the age range of 1 month to 3 years, 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.

Maintenance of anaesthesia

Maintenance of the required depth of anaesthesia can be achieved with the administration of Propofol 10mg/ml by means of an infusion or repeated bolus administration. 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/kg of body mass per hour. In the case of younger children, especially those in the age range of 1 month to 3 years, the required dose may be higher.

Lower doses are recommended for patients in the risk groups ASA III and IV.

Sedation of patients over 16 years of age during intensive care:

For the sedation of ventilated patients during intensive care, Propofol should be administered as a continuous infusion. The dosage is based on the required 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. Propofol may not be used for the sedation of children aged 16 years or younger as part of intensive care.

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

Sedation of adults for surgical and diagnostic procedures:

During the administration of Propofol, 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 -5 minutes. For the maintenance 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 mass per hour.

In addition to the infusion, 10 – 20 mg may be injected as a bolus if a quick increase in the depth of sedation is necessary.

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. 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 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 1 month of age for surgical and diagnostic procedures
The dosage and the periods between doses are selected based on the desired 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 the sedation is achieved with the titration of Propofol via an infusion until the desired depth of sedation is reached. For most patients, 1.5 - 9 mg Propofol /kg of body mass per hour is required. The infusion can be supplemented with bolus administration of up to 1 mg Propofol/kg of body mass, if a rapid increase in the depth of sedation is required.
Lower doses may be necessary for patients in the risk groups ASA III and IV.

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

Method of administration
Propofol 1% has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to Propofol 1%.
Propofol 1% can be used for infusion undiluted from glass containers, plastic syringes or Propofol 1% pre-filled syringes or diluted with 5% Dextrose (Intravenous Infusion BP) only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per ml) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.
It is recommended that, when using diluted Propofol 1%, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by Propofol 1% emulsion.
The dilution may be used with a variety of infusion control techniques, but a giving set used alone will not avoid the risk of accidental uncontrolled infusion of large volumes of diluted Propofol 1%. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of Propofol 1% in the burette.

When Propofol 1% is used undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.
Propofol 1% may be administered via a Y-piece close to the injection site into infusions of the following:
• Dextrose 5% Intravenous Infusion B.P.
• Sodium Chloride 0.9% Intravenous Infusion B.P.
• Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion B.P.
Propofol 1% may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.
In order to reduce pain on initial injection, Propofol 1% may be mixed with preservative-free Lidocaine Injection 0.5% or 1%.

Target Controlled Infusion - Administration of Propofol 1% by a 'Diprifusor' TCI System in Adults
Administration of Propofol 1% by a 'Diprifusor' TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.
Propofol 1% may be administered by TCI only with a 'Diprifusor' TCI system incorporating 'Diprifusor' TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing Propofol 1% or 2% Injection. The 'Diprifusor' TCI system will automatically adjust the infusion rate for the concentration of Propofol recognised. Users must be familiar with the infusion pump users' manual, and with the administration of Propofol 1% by TCI and with the correct use of the syringe identification system.
The Diprifusor allows the anaesthetist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol. An alternative effect-site mode of administration may be accessible on some Diprifusors, but its safety and efficacy have not yet been established.
The 'Diprifusor' TCI system assumes that the initial blood propofol concentration in the patient is zero. Therefore, in patients who have received prior propofol, there may be a need to select a lower initial target concentration when commencing 'Diprifusor' TCI. Similarly, the immediate recommencement of 'Diprifusor' TCI is not recommended if the pump has been switched off.
Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

Induction and Maintenance of General Anaesthesia
In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4–8 microgram/ml. An initial target of 4 microgram/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 microgram/ml is advised. Induction time with these targets is generally within the range of 60–120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.
A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration can then be increased in steps of 0.5–1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.
Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3–6 microgram/ml usually maintain satisfactory anaesthesia.

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

Dilution and Co-Administration of Propofol 1% with Other Drugs or Infusion Fluids

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing.	Dextrose 5% Intravenous Infusion	Mix 1 part of Propofol 1% with up to 4 parts of Dextrose 5% Intravenous Infusion B.P in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of Propofol 1%.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lidocaine hydrochloride injection (0.5% or 1% without preservatives).	Mix 20 parts of Propofol 1% with up to 1 part of either 0.5% or 1% lidocaine hydrochloride injection.	Prepare mixture aseptically immediately prior to administration. Use for Induction only.
	Alfentanil injection (500 microgram/ml).	Mix Propofol 1% with alfentanil injection in a ratio of 20:1 to 50:1 v/v.	Prepare mixture aseptically; use within 6 hours of preparation.
Co-administration via a Y-piece connector.	Dextrose 5% intravenous infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Sodium chloride 0.9% intravenous infusion	As above	As above
	Dextrose 4% with sodium chloride 0.18% intravenous infusion	As above	As above

4.3 Contraindications

Do not use Propofol

• in the case of hypersensitivity to active substance, soybeans, peanuts, or to any of the other ingredients of the emulsion listed in section 'List of excipients',

• for the sedation of patients aged 16 years or younger as part of intensive care.

4.4 Special warnings and precautions for use

During the use of Propofol 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 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 10mg/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, 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 are usually not observed for longer than 12 hours. When explaining the effect of Propofol 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 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.

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 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. 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 when Propofol 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.

When using Propofol 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.

Paediatric Population

The use of Propofol in newborns is not recommended, since this patient group has not been sufficiently evaluated. Pharmacokinetic data 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 occur and lead to severe circulatory and respiratory depression.

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.

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 discontinue the use of propofol 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 fatcontaining emulsions should be used with caution.

A check of the lipid metabolism parameters is recommended if Propofol is used in patients, where there is the suspicion of elevated blood lipid values. The administration of Propofol 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 should be taken into account. 1.0 ml Propofol 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 does not contain any antimicrobial preservation media, and the growth of microorganisms is facilitated due to its composition.

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

Propofol contains soybean oil, which may trigger severe allergic reactions very rarely.

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

4.5 Interaction with other medicinal products and other forms of interaction

Propofol is compatible with other agents for anaesthesia (premedication, muscle relaxants, inhaled anaesthesia, analgesics, local anaesthetics). In the case of regional anaesthesia procedures, smaller doses of Propofol 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 effects with the use of Propofol. 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 of in the propofol dose may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of propofol during pregnancy has not been proven. Therefore, Propofol should only be used during pregnancy if absolutely necessary. Propofol crosses the placenta and may be associated with the depression of vital functions in newborns. Propofol can be employed as anaesthesia in the case of termination of pregnancy.

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

Breast-feeding

Studies 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, 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. The impairments caused by Propofol are usually not observed for longer than 12 hours. The patient may only return home when 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, type of procedure and the therapeutic measures taken. The frequency of the occurrence of undesirable effects is based on the following categories.

The following definitions of frequencies are used:

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) and not known (cannot be estimated from the available data).

Table of Adverse Drug Reactions

System Organ Class	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 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
	Not known	Involuntary movements
Cardiac disorders	Common	Bradycardia[1]
	Very rare	Pulmonary oedema
	Not known	Cardiac arrhythmia[5], cardiac 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 disorders	Common	Singultation during the induction, nausea and vomiting during the waking phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known	Hepatomegaly[5]
Musculoskeletal and connective tissue disorders	Not known	Rhabdomyolysis [3,5]
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Not known	Renal failure[5]
Reproductive system 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 after 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 necessary.

[3] Rhabdomyolysis was reported very rarely if Propofol 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.

[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.

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 or/and plasma substitution and vasoconstrictors.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Other general anaesthetics,

ATC-code N0IAXI0.

After intravenous injection of Propofol, 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 GABAA receptors.

When the dosing guidelines are followed, a clinically relevant accumulation of propofol after multiple repeated injections or infusion can be ruled out.

Limited studies on the duration of action of anaesthesia with propofol in children indicate that the safety and efficacy remain unchanged up to duration 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.

Most patients awake quickly in a clearly conscious state.

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 in the 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 halflife 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 2.6-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 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 2-3x 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 crosses the placenta. Embryo toxicity studies in rats and rabbits did not provide any indication of a teratogenic effect.

Propofol 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

Soyabean oil BP
Glycerol BP
Egg Lecithin
Disodium Edetate BP
Sodium Oleate IH
Water for injection BP…Q.S.

6.2 Incompatibilities

This medicinal product must not be mixed with other products except those mentioned in section 'Special precautions for disposal and other handling'. The muscle relaxants, Atracurium and Mivacurium should not be administered through the same intravenous access as Propofol without first rinsing it out.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Shake well before use.

6.5 Nature and contents of container

Propofol Injection BP 1 % w/v is available in 100mg/10ml & 200mg/20ml.

6.6 Special precautions for disposal and other handling

For single use only.
Containers should be shaken before use.
Propofol should only be mixed with the following products: 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.
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 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.

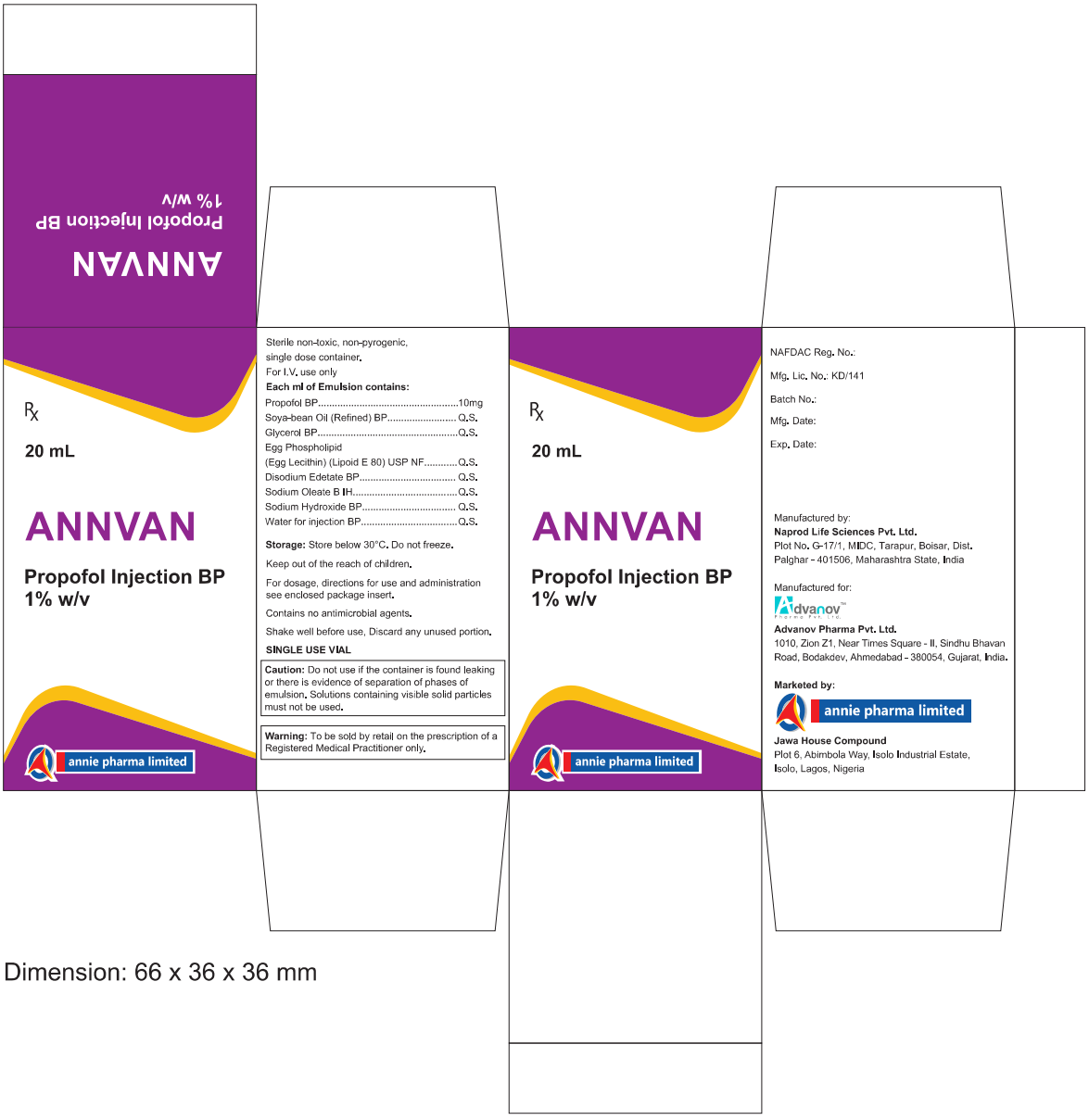
7. Marketing authorisation holder
<< maketing authorisation holder details >>

8. Marketing authorisation number(s)
<< marketing authorisation number details >>

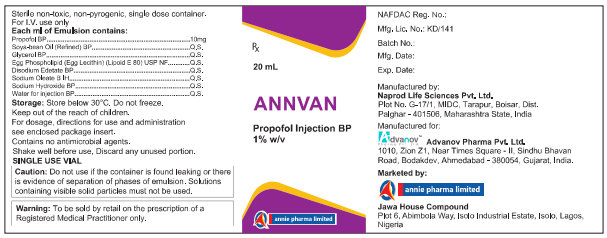
9. Date of first authorisation/renewal of the authorisation
<< date of authorisation/renewal >>

10. Date of revision of the text
06-Dec-2022

Company Contact Details
Naprod Life Sciences Pvt. Ltd.
Factory: G-17/1, MIDC, Tarapur, Boisar,
Dist. – Palghar – 401 506,
Maharashtra, INDIA.
Tel.: +91 2525 661110/ 661111



Dimension: 66 x 36 x 36 mm



Dimension: 79 x 30 mm

Enlarge size

Sterile non-toxic, non-pyrogenic, single dose container.
For I.V. use only
Each ml of Emulsion contains:
Propofol BP.....10mg
Soya-bean Oil (Refined) BP.....Q.S.
Glycerol BP.....Q.S.
Egg Phospholipid (Egg Lecithin) (Lipoid E 80) USP NF.....Q.S.
Disodium Edetate BP.....Q.S.
Sodium Oleate B IH.....Q.S.
Sodium Hydroxide BP.....Q.S.
Water for injection BP.....Q.S.
Storage: Store below 30°C. Do not freeze.
Keep out of the reach of children.
For dosage, directions for use and administration
see enclosed package insert.
Contains no antimicrobial agents.
Shake well before use, Discard any unused portion.
SINGLE USE VIAL

Caution: Do not use if the container is found leaking or there is evidence of separation of phases of emulsion. Solutions containing visible solid particles must not be used.

Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.

Rx

20 mL

ANNVAN

Propofol Injection BP
1% w/v

annie pharma limited

NAFDAC Reg. No.:

Mfg. Lic. No.: KD/141

Batch No.:

Mfg. Date:

Exp. Date:

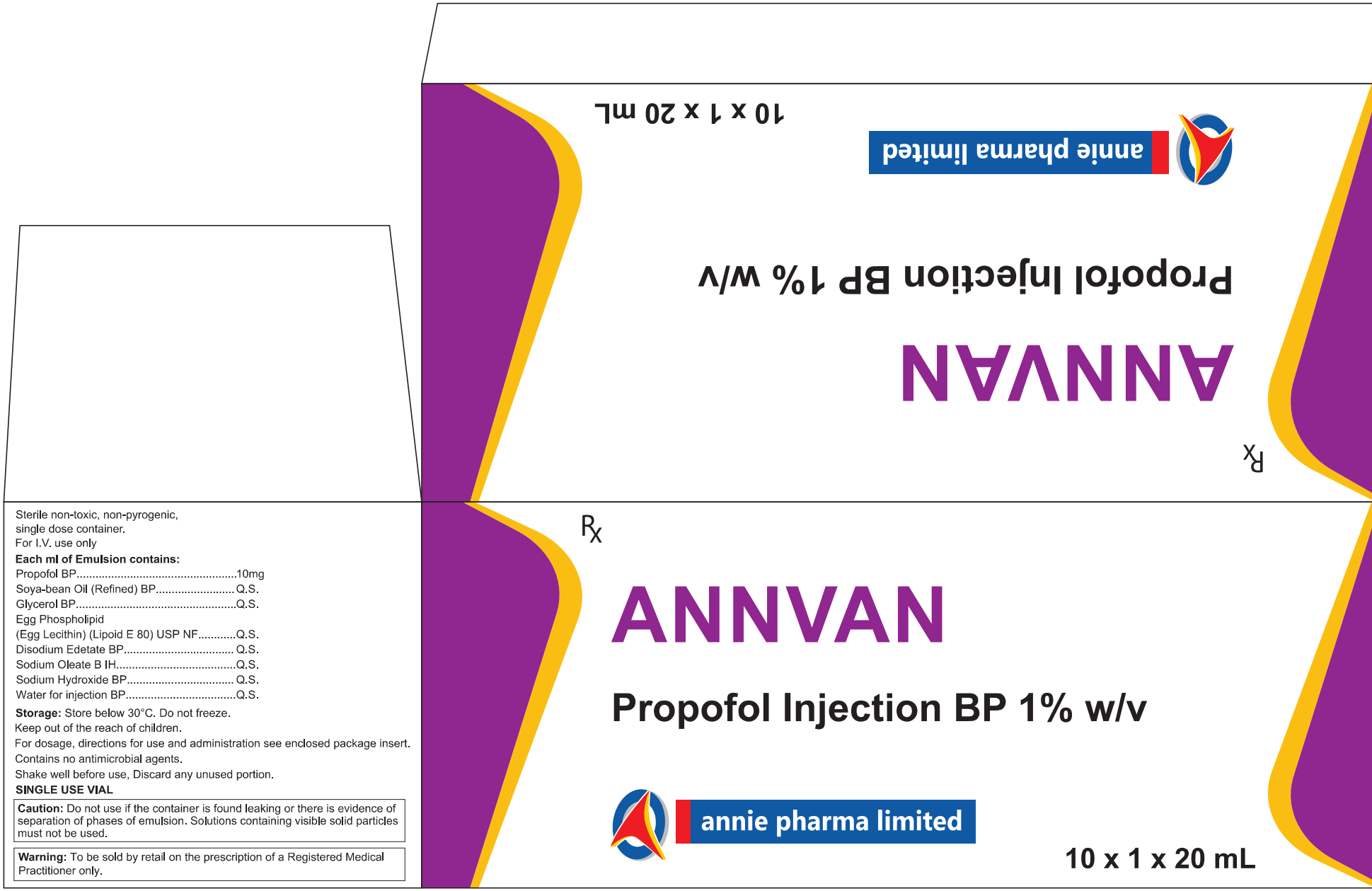
Manufactured by:
Naprod Life Sciences Pvt. Ltd.
Plot No. G-17/1, MIDC, Tarapur, Boisar, Dist.
Palghar - 401506, Maharashtra State, India

Manufactured for:
Advanov Pharma Pvt. Ltd.
1010, Zion Z1, Near Times Square - II, Sindhu Bhavan
Road, Bodakdev, Ahmedabad - 380054, Gujarat, India.

Marketed by:
annie pharma limited

Jawa House Compound
Plot 6, Abimbola Way, Isolo Industrial Estate, Isolo, Lagos,
Nigeria

Dimension: 79 x 30 mm



Dimension: 188 x 72 x 78 mm

105 x 230 mm Front

105 x 230 mm Back

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER
PROPOFOL INJECTION BP 1% W/V (ANNVAN)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again before, during or after use of this medicine.
- If you have any further questions, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please inform your health care provider.

In this leaflet:

1. WHAT PROPOFOL INJECTION BP 1% W/V IS AND WHAT IT IS USED FOR

ANNVAN contains a medicine called propofol. This belongs to a group of medicines called 'general anaesthetics'. General anaesthetics are used to cause unconsciousness (sleep) so that surgical operations or other procedures can be performed. They can also be used to sedate you (so that you are sleepy but not completely asleep).

ANNVAN will be given to you as an injection by a doctor.

In adults and children over 1 month of age it is used to:
- Help put you to sleep before an operation or other procedure.
- Keep you asleep during an operation or other procedure.
- Sedate you during diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia.

In people over 16 years of age it is also used to:
- Sedate you when receiving artificial respiration in an Intensive Care Unit (ICU).

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN PROPOFOL INJECTION BP 1% W/V

Do not use ANNVAN:
- If you are allergic to propofol or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to peanut or soya. This is because ANNVAN contains soya oil.
- If you are 16 years of age or younger for sedation in intensive care.

If any of the above apply to you, do not have ANNVAN and tell your doctor, anaesthetist or nurse. If you are not sure, talk to one of these people before having ANNVAN.

Warnings and precautions
The use of ANNVAN is not recommended in newborn infants.
Talk to your doctor, anaesthetist or nurse before using ANNVAN.

Before you have this medicine, tell your doctor, anaesthetist or nurse
- If you have ever had a fit or convulsion.
- If you have ever been told that you have very high levels of fat in your blood.
- If you have ever been told that your body has problems using fat.
- If your body has lost lots of water (you are dehydrated).
- If you have any other health problems, such as problems with your heart, breathing, kidneys or liver.
- If you have been generally unwell for some time.
- If you have mitochondrial disease.

Studies in young animals and clinical data suggest that repeated or lengthy use of general anaesthetics or sedation drugs in children younger than 3 years or in pregnant women during their third trimester may have negative effects on the development of the child's brain. Parents and caregivers should discuss the benefits, risks, timing and length of surgery or procedures requiring anaesthetics or sedation with your doctor.
If you are not sure if any of the above apply to you, talk to your doctor or nurse before having ANNVAN.

In rare cases, when receiving propofol over a prolonged period, you may develop a condition called Propofol Infusion Syndrome (PIS). This can harm your heart, muscles, kidneys, cause other serious problems, and may result in death. However, your doctor will monitor you closely and take steps to prevent this from happening.

Other medicines and ANNVAN
Tell your doctor if you are taking or have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines.

In particular, tell your doctor, anaesthetist or nurse if you are taking any of the following medicines:
- Rifampicin (for tuberculosis – TB)
- Midazolam (used to induce sedation – a very relaxed state of calm, drowsiness or sleep – and to relieve anxiety and muscle tension)

Pregnancy and breast-feeding
Do not have ANNVAN if you are pregnant unless absolutely necessary.

Studies have shown that small amounts of propofol can pass into breast milk. Therefore, you should not breastfeed your baby for 24 hours after taking propofol.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

After having propofol, you may still feel sleepy for some time. Do not drive or use any tools or machines until you are sure the effects have worn off.
- If you are able to go home shortly after having ANNVAN, do not drive a car or use any tools or machines.
- Ask your doctor when you can start doing these activities again and when you can go back to work.

ANNVAN contains sodium, soya oil and disodium edetate
ANNVAN contains sodium. If you are on a sodium-controlled diet, you will need to take this into account.

ANNVAN contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

ANNVAN contains disodium edetate. During prolonged use of ANNVAN for intensive care, you may need to be given a zinc (a mineral) supplement.

3. HOW PROPOFOL INJECTION BP 1% W/V IS GIVEN

You will be given ANNVAN by a doctor. It will be given to you as an injection into a vein. This is usually in the back of your hand or in your forearm.
- The doctor will give you the injection using a needle or through a fine plastic tube called a 'cannula'.
- The doctor can also use an electric pump to control how fast the injection is given. This may be done if you are having a long operation or if you are in an Intensive Care Unit. The dose of ANNVAN varies from one patient to another. The amount of propofol that you need depends on your age, size, physical fitness and the level of sleepiness or sleep that you need. The doctor will give you the correct dose to start and to sustain anaesthesia or to achieve the required level of sedation, by carefully watching your responses and vital signs (pulse, blood pressure, breathing etc.).

You may need several different medicines to keep you asleep or sleepy, free from pain, breathing in a healthy way and to keep your blood pressure steady. The doctor will decide which medicines you need and when you need them.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects although not everybody gets them.

Side effects that can happen during anaesthesia

The following side effects can happen during anaesthesia (while the injection is being given to you or when you are sleepy or asleep). Your doctor will be looking out for these. If they happen, your doctor will give you appropriate treatment.

Very common (may affect more than 1 in 10 people)
- A feeling of pain at the site of the injection (while the injection is being given, before you fall asleep).

Common (may affect up to 1 in 10 people)
- Low blood pressure.
- Changes in your breathing pattern.
- Slow heart beat.

Rare (may affect up to 1 in 1,000 people)
- Twitching and shaking of your body, or a fit (may also happen when you wake up).
- Unusual colour of urine (may also happen when you wake up).

Very rare (may affect up to 1 in 10,000 people)
- Allergic reactions.
- Stopping of your heart beat.
- Build up of fluid in the lungs which can make you very breathless (may also happen when you wake up).
- Anaphylactic shock

Not known: frequency cannot be estimated from the available data
- Shallow breathing.
- Prolonged, often painful erection (priapism).

Side effects that can happen after anaesthesia
The following side effects can happen after anaesthesia (when you are waking up or after you have woken up).

Common (may affect up to 1 in 10 people)
- Feeling sick (nausea).
- Being sick (vomiting).
- Headache.

Uncommon (may affect up to 1 in 100 people)
- Swelling and redness along a vein or blood clots.

Very rare (may affect up to 1 in 10,000 people)
- Feeling sexually aroused.
- High temperature (fever).
- Redness or soreness where the injection was given.
- Being unconscious after the operation. (When this has happened, the patients have recovered without problems.)
- Tissue damage.

Not known: frequency cannot be estimated from the available data
- A feeling of pain at the site of the injection.
- Swelling at the site of injection.
- Prolonged, often painful erection (priapism).
- Hepatitis (inflammation of the liver), acute liver failure (symptoms can include yellowing skin and eyes, itching, dark coloured urine, stomach pain and liver tenderness (indicated by pain under the front of the rib cage on your right-hand side), sometimes with loss of appetite).

Other possible side effects
The following side effects have been seen when propofol is used in intensive care at higher doses than recommended.

Very rare (may affect up to1 in 10,000 people)
- Heart failure.
- Inflamed pancreas (pancreatitis) which causes severe stomach pain.
- Too much acid in your blood. This may make you breathe more quickly.
- Increased amount of potassium in your blood.
- High blood level of a type of fat called lipids.
- Abnormal heart beat.
- Enlargement of the liver.
- Kidney failure.

The following side effects have been seen in children in intensive care when propofol has been stopped suddenly.

Common (may affect up to 1 in 10 people)
- 'Withdrawal symptoms'. These include unusual behaviour, sweating, shaking and feeling anxious.
- Flushing of the skin.

Do not be concerned by this list of possible side effects. You may not get any of them.

Not known: frequency cannot be estimated from the available data
- Euphoric mood.
- Involuntary movements.
- Drug abuse and dependence on propofol, mostly by healthcare professionals.
- Abnormal ECG.
- Breakdown of muscle cells (rhabdomyolysis).

If you think you have a side effect or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE PROPOFOL INJECTION BP 1% W/V

- Keep this medicine out of the sight and reach of children.
- The doctor and hospital pharmacist are responsible for storing, using and disposing of ANNVAN correctly.
- Store below 30°C. Do not freeze.
- Do not use ANNVAN after the expiry date which is stated on the carton after EXP.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Propofol Injection BP 1% w/v contains
The active substance is Propofol BP.
The other ingredients are: Soyabean Oil (Refined) BP, Egg phospholipid (Egg Lecithin) (Lipoid E 80) USP NF, Glycerol BP, Disodium Edetate BP, Sodium Oleate B IH, Sodium Hydroxide BP and Water for Injection BP.

What Propofol Injection BP 1% w/v looks like and contents of the pack
ANNVAN is a Milky white Emulsion packed in 20ml 20mm Flint tubular Type-I vials plugged with 20mm grey bromo butyl rubber stopper Biolcean; sealed with aluminium seal F/O top transparent yellow.

Manufactured by:
Naprod Life Sciences Pvt. Ltd.
Plot No. G-17/1, MIDC, Tarapur, Boisar, Dist. Palghar – 401506, Maharashtra State, India

Manufactured for:
Advanov Pharma Pvt. Ltd.
1010, Zion Z1, Near Times Square-II, Sindhu Bhavan Road, Bodakdev, Ahmedabad – 380054, Gujarat, India

Marketed by:
Annie Pharma Limited
Jawa House Compound Plot 6, Abimbola Way, Isolo Industrial Estate, Isolo, Lagos, Nigeria