Package leaflet: Information for the user

Diprivan 10 mg/ml (1%) Emulsion for Injection or Infusion

propofol

Read all of this leaflet carefully before you start having this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

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What is in this leaflet

1. What Diprivan is and what it is used for

Diprivan 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).
Diprivan 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 use Diprivan

Do not use Diprivan:
- 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 Diprivan 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 Diprivan and tell your doctor, anaesthetist or nurse. If you are not sure, talk to one of these people before having Diprivan.

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

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 Diprivan.

Other medicines and Diprivan
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)

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

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

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 Diprivan, 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 Diprivan, 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.

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

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

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

3. How to use Diprivan

You will be given Diprivan 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 Diprivan varies from one patient to another. The amount of Diprivan 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).

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).

Other possible side effects
The following side effects have been seen when Diprivan 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 Diprivan 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 Diprivan, 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.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Diprivan

- Keep this medicine out of the sight and reach of children.
- The doctor and hospital pharmacist are responsible for storing, using and disposing of Diprivan correctly.
- Store Diprivan between 2°C and 25°C. Do not freeze.
- Do not use Diprivan after the expiry date which is stated on the carton after EXP.

6. Contents of the pack and other information

What Diprivan contains

The active substance is propofol. There is 10 mg of propofol in each millilitre.
The other ingredients are glycerol, purified egg phosphatide, sodium hydroxide, soya bean oil, water for injections, nitrogen and disodium edetate.

What Diprivan looks like and contents of the pack
Diprivan 1% is a milky, white liquid. It comes in glass ampoules of 20 ml, glass vials of 50 ml or 100 ml, or pre-filled syringes of 20 ml or 50 ml.

Medical Information Leaflet

Diprivan 1%

(Issued to the Medical Professions Only)

1. Trade Name of the Medicinal Product

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

2. Qualitative and Quantitative Composition

Propofol 10 mg/ml Excipient(s) with known effect:
Soya-bean Oil, Refined Ph Eur

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Emulsion for injection or infusion.
White aqueous isotonic oil-in-water emulsion.

4. Clinical Particulars

4.1 Therapeutic indications

Diprivan 1% is a short-acting intravenous general anaesthetic for:
- Induction and maintenance of general anaesthesia in adults and children >1 month.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children >1 month.
- Sedation of ventilated patients >16 years of age in the intensive care unit.

4.2 Posology and method of administration

For specific guidance relating to the administration of Diprivan 1% with a target controlled infusion (TCI) device, which incorporates Diprifusor TCI software, (see Section 4.2.5). Such use is restricted to induction and maintenance of anaesthesia in adults. The Diprifusor TCI system is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

- Posology

Induction of general anaesthesia

Adults
In unpremedicated and premedicated patients, it is recommended that Diprivan 1% should be titrated (approximately 4 ml [40 mg] every 10 seconds in an average healthy adult by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients aged less than 55 years are likely to require 1.5–2.5 mg/kg of Diprivan 1%. The total dose required can be reduced by lower rates of administration (2–5 ml/min [20–50 mg/min]). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 2 ml [20 mg] every 10 seconds).
Elderly
In older people the dose requirement for induction of anaesthesia with Diprivan 1% is reduced. The reduction should take into account the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response.

Paediatric population
Diprivan 1% is not recommended for induction of anaesthesia in children aged less than 1 month.
For induction of anaesthesia in children over 1 month of age, Diprivan 1% 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/kg body weight of Diprivan 1% for induction of anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher (2.5–4 mg/kg body weight).

For ASA 3 and 4 patients lower doses are recommended (see also Section 4.4).
Administration of Diprivan 1% by a Diprifusor TCI system is not recommended for induction of general anaesthesia in children.

Maintenance of general anaesthesia

Adults
Anaesthesia can be maintained by administering Diprivan 1% either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia. Recovery from anaesthesia is typically rapid and it is therefore important to maintain Diprivan 1% administration until the end of the procedure.
- Continuous infusion

The required rate of administration varies considerably between patients, but rates in the region of 4–12 mg/kg/h usually maintain satisfactory anaesthesia.
- Repeat bolus injections

If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml) to 50 mg (5 ml) may be given according to clinical need.

Elderly
When Diprivan 1% is used for maintenance of anaesthesia the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

Paediatric population
Diprivan 1% is not recommended for maintenance of anaesthesia in children aged less than 1 month.Anaesthesia can be maintained in children over 1 month of age by administering Diprivan 1% by infusion or repeated bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients, but rates in the region of 9–15 mg/kg/h usually achieve satisfactory anaesthesia. In younger children, especially between the age of 1 month and 3 years, dose requirements may be higher.

For ASA 3 and 4 patients lower doses are recommended (see also Section 4.4).Administration of Diprivan 1% by a Diprifusor TCI system is not recommended for maintenance of general anaesthesia in children.

Sedation during intensive care

Adults
For sedation during intensive care it is advised that Diprivan 1% should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3–4 mg/kg/h of Diprivan 1% (see 4.4 Special warnings and special precautions for use). Diprivan 1% is not indicated for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications). Administration of Diprivan 1% by Diprifusor TCI system is not advised for sedation in the intensive care unit.
Diprivan 1% may be diluted with 5% Dextrose (see Dilution and Co-administration table below).
It is recommended that blood lipid levels be monitored should Diprivan 1% be administered to patients thought to be at particular risk of fat overload. Administration of Diprivan 1% 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 Diprivan 1% formulation; 1 ml of Diprivan 1% 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.

Elderly
When Diprivan 1% is used for sedation the rate of infusion should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

Paediatric population
Diprivan 1% is contraindicated for the sedation of ventilated children aged 16 years or younger receiving intensive care.

Sedation for surgical and diagnostic procedures

Adults
To provide sedation for surgical and diagnostic procedures, rates of administration should be individualised and titrated to clinical response.
Most patients will require 0.5–1 mg/kg over 1–5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating Diprivan 1% infusion to the desired level of sedation – most patients will require 1.5–4.5 mg/kg/h. In addition to the infusion, bolus administration of 10–20 mg may be used if a rapid increase in the depth of sedation is required. In patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

Administration of Diprivan 1% by a Diprifusor TCI system is not recommended for sedation for surgical and diagnostic procedures.

Elderly people
When Diprivan 1% is used for sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in older people as this may lead to cardiorespiratory depression.

Paediatric population
Diprivan 1% is not recommended for surgical and diagnostic procedures in children aged less than 1 month.

In children over 1 month of age, doses and administration rates should be adjusted according to the required depth of sedation and the clinical response. Most paediatric patients require 1–2 mg/kg body weight of Diprivan 1% for onset of sedation. Maintenance of sedation may be accomplished by titrating Diprivan 1% infusion to the desired level of sedation. Most patients require 1.5–9 mg/kg/h Diprivan 1%. The infusion may be supplemented by bolus administration of up to 1 mg/kg body weight if a rapid increase of depth of sedation is required. In ASA 3 and 4 patients lower doses may be required. Method of administration
Diprivan 1% has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to Diprivan 1%.

Diprivan 1% can be used for infusion undiluted from glass containers, plastic syringes or Diprivan 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 Diprivan 1%, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by Diprivan 1% emulsion (see Dilution and co-administration table below).

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 Diprivan 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 Diprivan 1% in the burette.
When Diprivan 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.

Diprivan 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.

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if Diprivan 1% is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

When the pre-filled syringe presentation is used in a syringe pump appropriate compatibility should be ensured.
In particular, the pump should be designed to prevent siphoning and should have an occlusion alarm set no greater than 1000 mm Hg. If using a programmable or equivalent pump that offers options for use of different syringes then choose only the B-D 50/60 ml PLASTIPAK setting when using the Diprivan 1% pre-filled syringe.

Diprivan 1% may be premixed with alfentanil injection containing 500 microgram/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, Diprivan 1% may be mixed with preservative-free Lidocaine Injection 0.5% or 1% (see Dilution and Co-administration table below).

Target Controlled Infusion – Administration of Diprivan 1% by a Diprifusor TCI System in adults Administration of Diprivan 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.

Diprivan 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 Diprivan 1% or 2% Injection. The Diprifusor TCI system will automatically adjust the infusion rate for the concentration of Diprivan recognised. Users must be familiar with the infusion pump users' manual, and with the administration of Diprivan 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 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 1–2 microgram/ml and will be influenced by the amount of analgesia given during maintenance.

Dilution and co-administration of Diprivan 1% with other drugs or infusion fluids (see also Additional precautions section)

Co- administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing	Dextrose 5% intravenous infusion	Mix 1 part of Diprivan 1% with up to 4 parts of dextrose 5% intravenous infusion 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 Diprivan 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 Diprivan 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 Diprivan 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Diprivan 1% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

Diprivan 1% must not be used in patients of 16 years of age or younger for sedation in intensive care (see section 4.4).

4.4 Special warnings and precautions for use

Diprivan 1% 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 patient airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Diprivan 1% should not be administered by the person conducting the diagnostic or surgical procedure.

Abuse of, and dependence on Diprivan 1%, predominantly by health care professionals, have been reported. As with other general anaesthetics, the administration of Diprivan 1% without airway care may result in fatal respiratory complications.

When Diprivan 1% 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 Diprivan 1% 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 Diprivan 1%. Very rarely the use of Diprivan 1% 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.

Diprivan 1% induced impairment is not generally detectable beyond 12 hours. The effects of Diprivan 1%, 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 (Eg, benzodiazepines, opiates, alcohol.)

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. Diprivan

1% clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Diprivan 1% clearance.

Diprivan 1% lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate, or when Diprivan 1% is used in conjunction with other agents likely to cause a bradycardia.

As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of Diprivan 1%.

During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.

Concomitant use of central nervous system depressants eg., alcohol, general anaesthetics, narcotic analgesics, will result in accentuation of their sedative effects. When Diprivan 1% is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that Diprivan 1% is administered following the analgesic and the dose should be carefully titrated to the patient's response (see Section 4.5).

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

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of Diprivan 1% during the period of anaesthetic maintenance.

When Diprivan 1% is administered to an epileptic patient, there may be a risk of convulsion.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously (see section 4.2).

Use is not recommended with electroconvulsive treatment.

As with other anaesthetics, sexual disinhibition may occur during recovery.

The benefits and risks of the proposed procedure should be considered prior to proceeding with repeated or prolonged use (>3 hours) of propofol in young children (< 3 years) and in pregnant women as there have been reports of neurotoxicity in preclinical studies, see Section 5.3.

Paediatric population

The use of Diprivan is not recommended in newborn infants as this patient population has not been fully investigated. Pharmacokinetic data (see section 5.2) indicate that clearance is considerably reduced in neonates and has a very high inter-individual variability. Relative overdose could occur on administering doses recommended for older children and result in severe cardiovascular depression.

Diprivan 2% is not recommended for use in children < 3 years of age due to difficulty in titrating small volumes.

Propofol must not be used in patients of 16 years of age or younger for sedation for intensive care as the safety and efficacy of propofol for sedation in this age group have not been demonstrated (see section 4.3).

Advisory statements concerning Intensive Care Unit management

Use of propofol emulsion infusions for ICU sedation has been associated with a constellation of metabolic derangements and organ system failures that may result in death. Reports have been received of combinations of the following: Metabolic acidosis, Rhabdomyolysis, Hyperkalaemia, Hepatomegaly, Renal failure, Hyperlipidaemia, Cardiac arrhythmia, Brugada-type ECG (elevated ST- segment and coved T-wave) and rapidly progressive Cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the Propofol Infusion Syndrome. These events were mostly seen in patients with serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or Diprivan 1% (usually at dose rates greater than 4mg/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), should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure (ICP) should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h.
Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload. Administration of propofol should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the propofol formulation; 1.0 mL of Diprivan contains approximately 0.1 g of fat.

Diprivan 1% contains 0.0018 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Additional precautions
Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentations of mitochondrial disease exacerbation and of the 'propofol infusion syndrome' may be similar.

Diprivan 1% contains no antimicrobial preservatives and supports growth of micro-organisms.

EDTA chelates metal ions, including zinc, and reduces microbial growth rates. The need for supplemental zinc should be considered during prolonged administration of Diprivan 1%, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

When Diprivan 1% 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 Diprivan 1% and infusion equipment throughout the infusion period. Any infusion fluids added to the Diprivan 1% line must be administered close to the cannula site. Diprivan 1% must not be administered via a microbiological filter.

Diprivan 1% and any syringe containing Diprivan 1% are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of Diprivan 1% must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of Diprivan 1% and the infusion line must be discarded and replaced as appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Diprivan 1% 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 Diprivan 1% may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques. Profound

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

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of Diprivan 1% (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Diprivan 1% during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Diprivan 1% should not be given to pregnant women except when absolutely necessary. Diprivan 1% can, however, be used during an induced abortion.
Obstetrics
Diprivan 1% crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

Breast-feeding
Studies of breastfeeding mothers showed that small quantities of Diprivan 1% are excreted in human milk. Women should therefore not breast-feed for 24 hours after administration of Diprivan 1%. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and use machines

Diprivan 1% has moderate influence on the 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 general anaesthesia.

Diprivan 1% induced impairment is not generally detectable beyond 12 hours (Section 4.4).

4.8 Undesirable effects

General
Induction and maintenance of anaesthesia or sedation 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 Diprivan 1% may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

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	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutrition disorders	Not known [9]	Metabolic acidosis [5], hyperkalaemia [5], hyperlipidaemia [5]
Psychiatric disorders	Not known [9]	Euphoric mood. Drug abuse and drug dependence [8]
Nervous system disorders	Common	Headache during recovery phase
	Rare	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
	Very rare	Postoperative unconsciousness
	Not known [9]	Involuntary movements
Cardiac disorders	Common	Bradycardia [1]
	Very rare	Pulmonary oedema
	Not known [9]	Cardiac arrhythmia [5], cardiac failure [5], [7]
Vascular disorders	Common	Hypotension [2]
	Uncommon	Thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Common	Transient apnoea during induction
	Not known [9]	Respiratory depression (dose dependent)
Gastrointestinal disorders	Common	Nausea and vomiting during recovery phase
	Very rare	Pancreatitis
Hepatobiliary disorders	Not known [9]	Hepatomegaly [5]
Musculoskeletal and connective tissue disorders	Not known [9]	Rhabdomyolysis [3], [5]
Renal and urinary disorders	Very rare	Discolouration of urine following prolonged administration
	Not known [9]	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 on induction [4]
	Very rare	Tissue necrosis [10] following accidental extravascular administration
	Not known [9]	Local pain, swelling, following accidental extravascular administration
Investigations	Not known [9]	Brugada type ECG [5], [6]
Injury, poisoning and procedural complications	Very rare	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 Diprivan.
(3) Very rare reports of rhabdomyolysis have been received where Diprivan 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 Diprivan 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.

Dystonia/dyskinesia have been reported.

Local
The local pain which may occur during the induction phase of Diprivan 1% anaesthesia can be minimised by the co-administration of lidocaine (see Dosage and Administration) and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

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: Other general anaesthetics ATC code: N01AX10

Mechanism of action
Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABAA receptors.

Pharmacodynamic effects
In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Diprivan 1% is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of Diprivan 1%, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

Diprivan 1% reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Clinical efficacy and safety
Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and postoperative nausea and vomiting.

In general, there is less postoperative nausea and vomiting following anaesthesia with Diprivan 1% than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol. Diprivan 1%, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Paediatric population
Limited studies on the duration of propofol based anaesthesia in children indicate safety and efficacy is unchanged up to duration of 4 hours. Literature evidence of use in children documents use for prolonged procedures without changes in safety or efficacy.

5.2 Pharmacokinetic properties

Absorption
When Diprivan 1% is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate.

Distribution
Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5– 2 litres/minute).

Elimination
The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2– 4 minutes), rapid elimination (half-life 30–60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.
After a single dose of 3 mg/kg intravenously, propofol clearance/kg body weight increased with age as follows: Median clearance was considerably lower in neonates <1 month old (n=25) (20 ml/kg/min) compared to older children (n= 36, age range 4 months–7 years). Additionally inter-individual variability was considerable in neonates (range 3.7–78 ml/kg/min). Due to this limited trial data that indicates a large variability, no dose recommendations can be given for this age group.

Median propofol clearance in older aged children after a single 3 mg/kg bolus was 37.5 ml/min/kg (4– 24 months) (n=8), 38.7 ml/min/kg (11–43 months) (n=6), 48 ml/min/kg (1–3 years)(n=12),
28.2 ml/min/kg (4–7 years)(n=10) as compared with 23.6 ml/min/kg in adults (n=6).

Linearity
The pharmacokinetics are linear over the recommended range of infusion rates of Diprivan 1%.

5.3 Preclinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans. In neonatal primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. The clinical significance of these nonclinical findings isn not known, and healthcare providers should balance the benefits of appropriate anaesthesia in young children less than 3 years of age and pregnant women who require procedures against the potential risks suggested by the preclinical data.. Propofol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. Pharmaceutical Particulars

6.1 List of excipients

Glycerol Ph. Eur Purified egg phosphatide
Sodium Hydroxide Ph. Eur Soya bean oil, Refined Ph. Eur
Water for injections Ph. Eur Nitrogen Ph. Eur
Disodium Edetate Ph. Eur

6.2 Incompatibilities

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as Diprivan 1% without prior flushing.

6.3 Shelf life

Shelf life of the product as packaged for sale
Ampoules: 3 years. Vials: 3 years. Pre-filled syringe: 2 years

Shelf life after dilution
Use of diluted Diprivan must begin immediately following dilution.

6.4 Special precautions for storage

Store between 2°C and 25°C. Do not freeze.

6.5 Nature and contents of container

a) Clear neutral glass ampoules of 20 ml in boxes of 5
b) Clear neutral glass vials of 50 ml and 100 ml
c) Type 1 glass pre-filled syringe of 50 ml

6.6 Special precautions for disposal and other handling

In-use precautions: Containers should be shaken before use. Any portion of the contents remaining after use should be discarded.
Diprivan 1% should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose or Lidocaine Injection (see Section 4.2.5).

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland.

Manufacturer:
Corden Pharma S.P.A, Viale dell'Industria 3, 20867 Caponago (MB), Italy

For general queries about this product, please contact: - AHC.Medinfo@ae.aspenpharma.com

For queries on medical information or Pharmacovigilance, please contact: - AHC.DrugSafety@ae.aspenpharma.com

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Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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