DIPRIVAN 10 mg/ml (1%)

propofol

Emulsion for injection or infusion

Composition
Propofol 10 mg/ml

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

Therapeutic indication
Diprivan is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

Diprivan may also be used for sedation of ventilated adult patients receiving intensive care.

Diprivan may also be used for conscious sedation for surgical and diagnostic procedures.

Posology and method of administration
Supplementary analgesic agents are generally required in addition to Diprivan.

Diprivan has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalation agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of Diprivan may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

Adults

Induction of general anaesthesia
Diprivan may be used to induce anaesthesia by slow bolus injection or infusion.

In unpremedicated and premedicated patients, it is recommended that Diprivan should be titrated (approximately 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 to 2.5 mg/kg of Diprivan. The total dose required can be reduced by lower rates of administration (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 20 mg every 10 seconds).

Maintenance of general anaesthesia
Anaesthesia can be maintained by administering Diprivan either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required.

Continuous Infusion: The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia.

Repeat Bolus Injections: If a technique involving repeat bolus injections is used, increments of 25 mg to 50 mg may be given according to clinical need.

as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

Diprivan may also be used diluted with 5% Dextrose Intravenous Infusion only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg Propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 6 hours.

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. 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 dilution in the burette.

Diprivan may be administered via a Y-piece close to the injection site, into infusions of Dextrose 5% Intravenous Infusion, Sodium Chloride 0.9% Intravenous Infusion or Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion.
Diprivan may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil ('Rapifen'; Janssen Pharmaceuticals Ltd.) 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.
To reduce pain on initial injection, Diprivan used for induction may be mixed with Lidocaine Injection in a plastic syringe in the ratio of 20 parts Diprivan with up to one part of either 0.5% or 1% Lidocaine Injection immediately prior to administration.

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 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.	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 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	Mix Diprivan with alfentanil	Prepare mixture aseptically; use

Sedation during intensive care
When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that Diprivan be given by continuous infusion. Infusion rates between 0.3 and 4.0 mg/kg/h achieve satisfactory sedation in most adult patients. Administration of DIPRIVAN for ICU sedation in adult patients should not exceed 4mg/kg/hour unless the benefits for the patient outweigh the risks (see Special warnings and special precautions for use).

Conscious sedation for surgical and diagnostic procedures
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 to 1 mg/kg over 1 to 5 minutes to initiate sedation.

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

Elderly Patients
In elderly patients the dose requirement for induction of anaesthesia with Diprivan is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Where Diprivan is used for maintenance of anaesthesia or 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 the elderly as this may lead to cardiorespiratory depression.

Children

Induction of general anaesthesia
Diprivan is not recommended for use in children less than 3 years of age (see section 'Undesirable effects').
When used to induce anaesthesia in children, it is recommended that Diprivan be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of Diprivan for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

Maintenance of general anaesthesia
Diprivan is not recommended for use in children less than 3 years of age.

Anaesthesia can be maintained by administering Diprivan by infusion or repeat 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 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

Conscious sedation for surgical and diagnostic procedures
Diprivan is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated.

Sedation during intensive care
Diprivan is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

Administration
Diprivan can be used for infusion undiluted from plastic syringes or glass infusion bottles. When Diprivan is used undiluted to maintain anaesthesia, it is recommended that equipment such

	micrograms/ml)	injection in a ratio of 20:1 to 50:1 v/v.	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

Contraindications
Diprivan is contraindicated in patients with a known hypersensitivity to propofol or any of the excipients.

Diprivan is not recommended in children under the age of 3 years.

Diprivan is contraindicated for the sedation of children of all ages with croup or epiglottitis receiving intensive care (See section 'Special warnings and special precautions for use').

Special warnings and special precautions for use
Diprivan should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care). Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. Diprivan should not be administered by the person conducting the diagnostic or surgical procedure.

When Diprivan 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 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 general anaesthesia. Very rarely the use of Diprivan 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.

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 lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of 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 is used in conjunction with other agents likely to cause a bradycardia.

When Diprivan 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.

It is recommended that blood lipid levels should be monitored if Diprivan is administered to patients thought to be at particular risk of fat overload. Administration of Diprivan 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 formulation; 1.0 ml of Diprivan contains approximately 0.1 g of fat.

Diprivan is not recommended for use in neonates for induction and maintenance of anaesthesia. Data from off-label use have indicated that if the dose regimen recommended for children (3 years to 16 years) is applied to neonates, a relative overdose could occur which may result in cardiorespiratory depression. (See sections 'Posology and method of administration' and 'Undesirable effects').

There are no data to support the use of Diprivan for the sedation of premature neonates receiving intensive care.
There are no clinical trials data to support the use of Diprivan for the sedation of children with croup or epiglottitis receiving intensive care.

Advisory statement concerning Intensive Care Unit management:
Very rare reports of metabolic acidosis, rhabdomyolysis, hyperkalaemia, and/or cardiac failure, in some cases with a fatal outcome, have been received concerning seriously ill patients receiving Diprivan for ICU sedation. The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological agents - vasoconstrictors, steroids, inotropes and/or propofol. All sedative and therapeutic agents used in the ICU (including Diprivan) should be titrated to maintain optimal oxygen delivery and haemodynamic parameters.

EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of Diprivan, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

Additional precautions
Diprivan contains no antimicrobial preservatives and supports growth of micro-organisms. When Diprivan 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 and infusion equipment throughout the infusion period. Any infusion fluids added to the Diprivan line must be administered close to the cannula site. Diprivan must not be administered via a microbiological filter.

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

Interactions with other medicinal products and other forms of interaction
Diprivan 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 may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

Pregnancy and lactation
Pregnancy
Diprivan should not be used in pregnancy. Diprivan has been used, however, during termination of pregnancy in the first trimester.

Obstetrics
Diprivan crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia.

Lactation
Safety to the neonate following the use of Diprivan in mothers who are breast feeding has not been established.

Reports from off-label use of Diprivan for induction of anaesthesia in neonates indicates that cardiorespiratory depression may occur if the paediatric dose regimen is applied.
(See sections 'Posology and method of administration' and 'Special warnings and special precautions for use').

Overdose
Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

Pharmacodynamic properties
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 $GABA_A$ receptors.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when Diprivan 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, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

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

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

In general, there is less post-operative nausea and vomiting following anaesthesiwith Diprivan than following anaesthesia with inhalational agents. There is evidence that this may be related to an antiemetic effect of propofol.

Diprivan, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetic properties
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. The first phase is characterised by a very rapid distribution (half-life 2-4 minutes) followed by

Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

Undesirable effects

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

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

(1) May be minimised by using the larger veins of the forearm and antecubital fossa. With Diprivan 1% local pain can also be minimised by the co-administration of lidocaine (see 'Posology and method of administration' 'administration' section).

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of Diprivan.

(3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(4) Following abrupt discontinuation of Diprivan during intensive care.

(5) Very rare reports of rhabdomyolysis have been received where Diprivan has been given at doses greater than 4 mg/kg/hr for ICU sedation.

by a very rapid distribution (half-life 2-4 minutes) followed by rapid elimination (half-life 30-60 minutes) and a slower final phase, representative ofredistribution of propofol from poorly perfused tissue.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5-2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

When Diprivan is used to maintain anaesthesia, blood concentrations of propofol asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of Diprivan.

List of excipients

Glycerol Ph.Eur.
Purified Egg Phosphatide
Sodium Hydroxide Ph.Eur.
Soya-bean Oil, Refined Ph.Eur.
Water for Injections Ph.Eur.
Disodium Edetate Ph. Eur.

Incompatibilities

Diprivan should not be mixed prior to administration with injections or infusion fluids other than with 5% Dextrose in PVC bags or glass infusion bottles or Lidocaine Injection or alfentanil injection in plastic syringes.

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

Shelf life

Please refer to expiry date on the ampoule or vial.

Special precautions for storage

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

Pack size

Please refer to the outer carton for pack size.

Instructions for use and handling

Containers should be shaken before use. Any portion of the contents remaining after use should be discarded.

Asepsis for Diprivan and infusion equipment must be maintained (see 'Additional precautions').

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