Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diprivan 1% w/v Emulsion for Injection or Infusion, Pre-filled Syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains propofol 10 mg/ml.

Each 20 ml pre-filled syringe contains 200 mg propofol.
Each 50 ml pre-filled syringe contains 500 mg propofol.

Excipient(s) with known effect:
Contains sodium 0.0018 mmol/ml.
Contains refined soya-bean oil 100 mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection or infusion.
White or almost white emulsion for injection or infusion, supplied in pre-filled syringes.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Diprivan is a short-acting intravenous general anaesthetic for:

- Induction and maintenance of general anaesthesia in adults and children over one month of age.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and children over one month of age.
- Sedation of ventilated patients over 16 years of age in the intensive care unit.

Diprivan may be administered by a Diprifusor TCI system for induction and maintenance of general anaesthesia and conscious sedation for surgical and diagnostic procedures in adults only. Administration of Diprivan by a Diprifusor TCI system is not recommended for any indication in children or adolescents under 16 years old. Administration of Diprivan by a Diprifusor TCI system is not recommended for intensive care sedation.

4.2 Posology and method of administration

Posology

Supplementary analgesic agents are generally required in addition to Diprivan.
For specific guidelines relating to the administration of Diprivan using the Diprifusor target controlled infusion (TCI) system, which incorporates Diprifusor TCI software, see section E. Such use is restricted to induction and maintenance of anaesthesia and conscious sedation for surgical and diagnostic procedures in adults. The Diprifusor TCI system is not recommended for use in ICU sedation, or in children or adolescents under 16 years old.

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

A) Adults
Induction of General Anaesthesia
Diprivan 1% 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 about 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: Diprivan 1% may be used. 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 Injection: If a technique involving repeat bolus injection is used, increments of 25 mg to 50 mg may be used according to clinical need.

Sedation of Ventilated Patient in the Intensive Care Unit
For sedation during intensive care it is advised that Diprivan 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 (see section 4.4). Diprivan is not indicated for sedation in intensive care of patients of 16 years of age or younger (see section 4.3). Administration of Diprivan by Diprifusor TCI system is not advised for sedation in the intensive care unit.

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 of ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

B) Elderly patients
In older people 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 older people as this may lead to cardiorespiratory depression.

C) Paediatric population
Diprivan is not recommended for use in children less than one month of age.

Administration of Diprivan by a Diprifusor TCI system is not recommended for any indication in children.

Induction of General Anaesthesia: 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).

Maintenance of General Anaesthesia: Anaesthesia can be maintained by administering Diprivan 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).

Conscious Sedation for Surgical and Diagnostic Procedures: 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.

D) Administration

Method of administration

Diprivan can be used for infusion undiluted from plastic syringes or glass infusion bottles or Diprivan pre-filled syringes. When Diprivan 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 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, 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 by 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.

In order to reduce pain on initial injection, Diprivan 1% used for induction may be mixed with Lidocaine Injection in a plastic syringe in the ratio of 20 parts Diprivan 1% with up to one part of 0.5 or 1% Lidocaine Injection immediately prior to administration.

Diprivan 1% 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 at room temperature and under normal lighting conditions.

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

Dilution and Co-administration of Diprivan with other Drugs or Infusion Fluids

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	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.

		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%.	
	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 micrograms/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

E) Target Controlled Infusion – Administration of Diprivan by Diprifusor TCI System in Adults
Diprivan may be administered by TCI with the Diprifusor TCI system incorporating Diprifusor TCI software. This system will operate only on recognition of electronically tagged pre-filled syringes containing Diprivan 1%. The Diprifusor TCI system will automatically adjust the infusion rate to achieve the concentration of Diprivan selected by the operator. Users must be familiar with the infusion pump user manual and with the administration of Diprivan by TCI and with the correct use of the syringe identification system.

The Diprifusor TCI system can provide two modes of target controlled infusion: target **blood** concentration and target **effect-site (brain)** concentration. Earlier models provide only the target blood concentration mode.

Administration of Diprivan by a Diprifusor TCI system is restricted to adults for the induction and maintenance of general anaesthesia and conscious sedation for surgical and diagnostic procedures. It is not recommended for use in ICU sedation or in children or adolescents under 16 years old.

The system allows control of induction and depth of anaesthesia or conscious sedation by setting and adjusting target (predicted) blood or effect-site concentrations of propofol. Use of the target effect-site concentration mode achieves a more rapid induction of sedation or anaesthesia than use of the target blood concentration mode.

The pharmacokinetic model in Diprifusor TCI system assumes that the initial target concentrations in the patient are zero. Therefore, in patients who have recently 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; if this has occurred, the Diprifusor TCI system indicates that it has been switched off by requiring re-entry/confirmation of patient data.

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 or conscious sedation required.

In adult patients under 55 years of age, anaesthesia can usually be induced with target **blood** propofol concentrations in the region of 4 to 8 micrograms/ml or target **effect-site** concentrations of 2.5 to 4 micrograms/ml. An initial target blood concentration of 4 micrograms/ml or target effect-site concentration of 2.5 micrograms/ml is recommended in premedicated patients and in unpremedicated patients an initial target blood concentration of 6 micrograms/ml or target effect-site concentration of 4 micrograms/ml is advised. Induction time with target blood concentrations is generally within the range of 60–120 seconds. Higher target blood concentrations will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression. When using target effect-site concentrations the use of higher targets to achieve more rapid induction of anaesthesia is not necessary and not recommended.

Lower initial target concentrations should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4 (use of effect-site mode in patients of ASA grade 4 is not recommended). For the effect-site mode an initial target of 0.5 to 1 micrograms/ml should be used. For both target concentration modes, the target can then be increased in steps of 0.5 to 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 blood concentrations in the region of 3 to 6 micrograms/ml and target effect-site concentrations of 2.5 to 4 micrograms/ml usually induced and maintain satisfactory anaesthesia. In the absence of supplementary analgesia, higher effect-site targets of 5 to 6 micrograms/ml may be required to facilitate laryngoscopy or to abolish responses to painful stimuli.

For both target concentration modes, the predicted propofol concentration (blood or effect-site) on waking is generally in the region of 1 to 2 micrograms/ml and will be influenced by the amount of analgesia given during maintenance. When target concentrations are reduced, the Diprifusor transiently stops the infusion to allow concentrations to fall and achieve a new target more quickly.

Conscious Sedation for Surgical and Diagnostic Procedures
The target concentration setting should be titrated against the response of the patient to achieve the depth of conscious sedation required.

An initial target **blood** propofol concentration in the range of 0.5 to 2.5 micrograms/ml will generally be required. Initial target blood concentrations towards the upper end of the recommended range will allow more rapid induction of conscious sedation.

In older people and in patients of ASA grades 3 and 4, initial target blood concentrations towards the lower end of the range should be used.

In young, healthy patients, an **effect-site** target of 1.5 to 2 micrograms/ml generally achieves satisfactory sedation, which is achieved more rapidly than when the target blood concentration control mode is used. When using target effect-site concentrations the use of higher targets to achieve more rapid induction of sedation is not necessary and not recommended. There is insufficient evidence to recommend use of effect-site mode for conscious sedation in older people or patients of ASA grades 3 or 4.

Routine oxygen supplementation should be provided.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Diprivan 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 is intended for use in hospitals only.

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 patient 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 surgical or diagnostic procedure.

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

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 use of Diprivan. 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.

Diprivan induced impairment is not generally detectable beyond 12 hours. The effects of Diprivan, 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 clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce Diprivan clearance.

Diprivan 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 is used in conjunction with other agents likely to cause 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.

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 for 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 (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 Diprivan 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.

Diprivan contains 0.0018 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet. Diprivan contains 100 mg refined soya-bean oil per ml.

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.

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 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, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

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.

4.5 Interaction with other medicinal products and other forms of interactions

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 or sedation 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 hypotensive effect of Diprivan may be potentiated by the concomitant administration of opiate analgesics. This effect may be more marked in elderly patients and when agents such as alfentanil are given by infusion.

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

A need for lower propofol doses has been observed in patients taking midazolam. The co-administration of propofol with midazolam is likely to result in enhanced sedation and respiratory depression. When used concomitantly, a dose reduction of propofol should to be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Diprivan during pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Diprivan should not be given to pregnant women except when absolutely necessary. Diprivan crosses the placenta and can cause neonatal depression. Diprivan can, however, be used during an induced abortion.
High doses (more than 2.5 mg/kg for induction or 6 mg/kg/h for maintenance of anaesthesia) should be avoided.

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

4.7 Effects on ability to drive and use machines

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

Diprivan induced impairment is not generally detectable beyond 12 hours (see section 4.4).

4.8 Undesirable effects

General
Induction and maintenance of anaesthesia or sedation is generally smooth with minimal evidence of excitation, although spontaneous movements may be seen in some patients. 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 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 Not known	Sexual disinhibition 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.

Local
The local pain which may occur during the induction phase can be minimised by the use of the larger veins in the forearm and antecubital fossa. With Diprivan 1% local pain can also be minimised by the co-administration of lidocaine (see section 4.2). 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
email: medsafety@hpra.ie

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 $GABA_A$ receptors.

Pharmacodynamic effects
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 quantitatively similar to those of the 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.

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 than following anaesthesia with inhalation agents.
Diprivan, 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 is used to maintain anaesthesia, blood concentrations of propofol 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. The first phase is characterised 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 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.

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. The clinical significance of these nonclinical findings in not known. Published studies in animals demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. 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. Data in foetal and neonatal rodents and primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. The clinical significance of these preclinical findings is 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

Soya-bean Oil, Refined
Purified Egg Phosphatide
Glycerol

Sodium Hydroxide (for adjustment of pH)
Disodium Edetate
Water for Injections

6.2 Incompatibilities

Diprivan should not be mixed prior to administration with injections or infusion fluids with the exception of Diprivan 1% which can be mixed with 5% Dextrose, in PVC bags or glass infusion bottles or Lidocaine Injection in plastic syringes and alfentanil injection *(see section 4.2)*.

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

6.3 Shelf life

Shelf life of the product as packaged for sale:
2 years (20 ml)
3 years (50 ml)

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
For storage precautions for diluted product, *see section 6.3 Shelf Life*.

6.5 Nature and contents of container

Type I glass pre-filled syringes containing 20ml or 50ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For more detailed administration instructions for Diprivan and mixtures of Diprivan, please *see section 4.2 Posology and Method of Administration*.

In-use precautions: Containers should be shaken before use. Any portion of the contents remaining after use should be discarded.

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 pre-filled syringe.

Asepsis for Diprivan and infusion equipment must be maintained (see Section 4.4 Warnings and precautions for use).

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th October 1995
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10 DATE OF REVISION OF THE TEXT

July 2021