Presentation
White aqueous isotonic oil-in-water emulsion for i.v. injection, containing 10 mg propofol per 1 ml, in a glass pre-filled syringe.

Indications
‘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.

Dosage 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.

For specific guidance 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 in adults. The ‘Diprifusor’ TCI system is not recommended for use in ICU sedation or conscious sedation, or in children.

A. 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.

Sedation during intensive care
Administration of ‘Diprivan’ by a ‘Diprifusor’ TCI system is not recommended for 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. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 to 4.0 mg/kg/h should achieve satisfactory sedation.

Conscious sedation for surgical and diagnostic procedures
Administration of ‘Diprivan’ by a ‘Diprifusor’ TCI system is not recommended for conscious sedation.

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.

B. 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.

C. Children

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

Induction of general anaesthesia

‘Diprivan’ is not recommended for use in children less than 3 years of age (see Section ‘Possible Adverse Reactions’).

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.

D. 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’ 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.

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.

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.

‘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 Lignocaine Injection in a plastic syringe in the ratio of 20 parts ‘Diprivan’ with up to one part of either 0.5% or 1% Lignocaine Injection immediately prior to administration.

Dilution and co-administration of ‘Diprivan’ with other drugs or infusion fluids
(See also ‘Additional Precautions’ Section)

<table>
<thead>
<tr>
<th>Co-administration Technique</th>
<th>Additive or Diluent</th>
<th>Preparation</th>
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<tbody>
<tr>
<td>Pre-mixing</td>
<td>Dextrose 5% Intravenous Infusion</td>
<td>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’.</td>
<td>Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.</td>
</tr>
</tbody>
</table>

Lignocaine Hydrochloride Injection. (0.5% or 1% without preservatives) Mix 20 parts of ‘Diprivan’ with up to 1 part of either 0.5% or 1% Lignocaine Hydrochloride Injection. Prepare mixture aseptically immediately prior to administration. Use for induction only.

Alfentanil injection (500 microgram/ml) Mix ‘Diprivan’ 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

Administration of ‘Diprivan’ 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 conscious sedation, or in children.

‘Diprivan’ 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’ 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’ by TCI and with the correct use of the syringe identification system, all of which are set out in the ‘Diprifusor’ training manual available from AstraZeneca.

The system allows the anaesthetist or intensivist to achieve and control a desired speed of induction
and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol. 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 to 8 micrograms/ml. An initial target of 4 micrograms/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 micrograms/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 concentrations can then be increased in steps of 0.5 to 1.0 micrograms/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 to 6 micrograms/ml usually maintain satisfactory anaesthesia.

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

Sedation During Intensive Care

Target blood propofol concentration settings in the range of 0.2 to 2.0 micrograms/ml will generally be required. Administration should begin at a low target setting which should be titrated against the response of the patient to achieve the depth of sedation desired.

Contra-indications

‘Diprivan’ is contra-indicated in patients with a known allergy to ‘Diprivan’.

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

‘Diprivan’ is contra-indicated for the sedation of children of all ages with croup or epiglottitis receiving intensive care (See Section ‘Warning and Precautions for Use’).

Warnings and 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 cardio-respiratory depression. (See Sections ‘Dosage and Method of Administration’ and ‘Possible Adverse Reactions’).

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. These reports demonstrated that a failure of oxygen delivery to the tissues was likely to have occurred. A causal relationship between these reported events and ‘Diprivan’ has not been established. 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 medicaments and other forms of interactions

‘Diprivan’ has been used in association with spinal and epidural anaesthesia and with commonlyused premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmaco-
logical 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.

**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.

**Possible adverse reactions**

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.

<table>
<thead>
<tr>
<th>Very common (&gt;1/10)</th>
<th>General disorders and administration site conditions:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vascular disorders: Cardiac disorders: Respiratory, thoracic and mediastinal disorders: Gastrointestinal disorders: Nervous system disorders: General disorders and administration site conditions:</td>
</tr>
<tr>
<td></td>
<td>Hypotension a(^{(1)}) Bradycardia a(^{(1)}) Transient apnoea during induction Nausea and vomiting during recovery phase Headache during recovery phase Withdrawal symptoms in children a(^{(2)}) Flushing in children a(^{(2)})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common (&gt;1/100, &lt;1/10)</th>
<th>Local pain on induction a(^{(1)})</th>
</tr>
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<tbody>
<tr>
<td>Vascular disorders:</td>
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<table>
<thead>
<tr>
<th>Uncommon (&gt;1/1000, &lt;1/100)</th>
<th>Vascular disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis and phlebitis</td>
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</table>

Reports from off-label use of Diprivan for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied (See Section ‘Dosage and Method of Administration’ and ‘Warning and Precautions for Use’).

**Overdosage**

Accidental overdosage is likely to cause cardio-respiratory 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.

**Pharmacological properties**

**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 anae-
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’.

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 Lignocaine 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.

Special precautions for storage
Store between 2°C and 25°C. Do not freeze.

Instructions for use/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’).

Shelf life
Please refer to expiry date on the syringe

Pack size
Please refer to the outer carton for pack size

Date of revision of the text
August 2004

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 rapid elimination (half-life 30-60 minutes) and a slower final phase, representative of redistribution 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.