IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0970/005/001
Case No: 2070848

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Diprivan 1% w/v Emulsion for Intravenous Injection or Infusion, 20ml ampoule

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/12/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diprivan 1% w/v Emulsion for Intravenous Injection or Infusion, 20ml ampoule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains Propofol 10mg/ml (200mg per 20ml ampoule).

Contains sodium 0.0018mmol/ml.
Contains refined Soya-bean oil 100mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection or infusion.

A white or almost white emulsion supplied in 20ml ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Diprivan is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia in adults and children over one month of age.

Diprivan may also be used for sedation of ventilated patients receiving intensive care in adults, only for a period of 48 hours, or in rare cases up to a maximum of 7 days.

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

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

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.Diprivan 2% should be used to induce anaesthesia by infusion and only in those patients who will receive Diprivan 2% for maintenance of anaesthesia.

In unpremedicated and premedicated patients, it is recommended that Diprivan should be titrated (approximately 40 mg every 10 seconds in an average healthy adult) 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% or Diprivan 2% 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: It is recommended that only Diprivan 1% is used. 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 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

Diprivan is not recommended for use in children less than one month of age. Diprivan 2% is not recommended for induction and maintenance of anaesthesia in children between 1 month and 3 years of age since the 2% strength is difficult to be accurately titrated in small children, due to the small volumes needed. For these patients it is recommended to use Diprivan 1%.

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

Induction of General Anaesthesia: When used to induce anaesthesia in children, it is recommended that Diprivan is 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: Anaesthesia can be maintained by administering Diprivan by infusion or repeat bolus injection to maintain the depth of anaesthesia required. It is recommended that only Diprivan 1% is used if repeat bolus injections are used. 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. Younger children, 1 month to 3 years, may have higher dosage requirements, within the range of recommended dosages, when compared with older paediatric patients. Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia.

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

Administration of Diprivan 2% by bolus injection is not recommended.

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 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 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 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) <u>Target Controlled Infusion – Administration of Diprivan by Diprifusor TCI System in Adults</u>
Administration of Diprivan by a Diprifusor TCI system is restricted to induction and maintenance of general anaesthesia and conscious sedation for surgical and diagnostic procedures in adults. It is not recommended for use in ICU sedation or in children or adolescents under 16 years old.

To achieve induction and maintenance of anaesthesia and conscious sedation for surgical and diagnostic procedures in adults, Diprivan may be administered with the assistance of a Target

Controlled Infusion (TCI) system. Such systems allow the anaesthetist or intensivist to achieve and control a desired speed of induction and depth of anaesthesia or conscious sedation by setting and adjusting target (predicted) blood concentrations of propofol. 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 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 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 at the address below.

The pharmacokinetic model in 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; 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 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 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 to 1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3 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.

Conscious Sedation for Surgical and Diagnostic Procedures

Target blood propofol concentration settings in the range of 0.5 to 2.5 micrograms/ml will generally be required. The target concentration setting should be titrated against the response of the patient to achieve the depth of conscious sedation required.

An initial target concentration towards the upper end of this range will allow more rapid induction of conscious sedation.

An initial target concentration towards the lower end of this range should be used in elderly patients and in patients of ASA grades 3 and 4.

Routine oxygen supplementation should be provided.

4.3 Contraindications

Known hypersensitivity for any of the components of Diprivan.

Diprivan is contraindicated for sedation in intensive care of patients of 16 years of age or younger *(see section 4.4).*

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

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 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 surgical or diagnostic 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 postoperative 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 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.

Propofol is not advised for general anaesthesia in children younger than 1 month of age. The safety and efficacy of Diprivan for (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure (in some cases with fatal outcome) in adults who were treated for more than 58 hours with dosages in excess of 5 mg/kg/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with raised ICP. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the Diprivan dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

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 be monitored should Diprivan be 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 paediatric (1 month to 16 years of age) dose regimen is applied in neonates, a relative overdose could occur which may result in cardiorespiratory depression *(see sections 4.2 and 4.8).*

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.

Diprivan contains 0.0018 mmol sodium per ml and 100mg refined soya-bean oil per ml.

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

4.5 Interaction 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. The hypotensive effect of propofol 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.

4.6 Pregnancy and lactation

Pregnancy: The safety of Diprivan during pregnancy has not been established, therefore, Diprivan should not be used in pregnant women unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression. High doses (more than 2.5mg/kg for induction or 6mg/kg/h for maintenance of anaesthesia) should be avoided.

Lactation: Safety to the neonate following the use of Diprivan in mothers who are breast-feeding has not been established. Studies in breast-feeding women showed that propofol is excreted in small amounts into the milk. Therefore, mothers should stop breast-feeding and discard breast milk for 24 hours after administration of propofol.

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.

4.8 Undesirable effects

General
Induction of anaesthesia 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 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
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 (4)
	Gastrointestinal disorders:	Pancreatitis
	Injury, poisoning and procedural complications:	Postoperative 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:	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 section 4.2, part D).*

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

In very rare cases rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, sometimes with fatal outcome, have been observed when Diprivan was administered at dosages in excess of 4 mg/kg/h for sedation in the intensive care unit *(see section 4.4).*

Reports from off-label use of Diprivan for induction of anaesthesia in neonates indicate that cardiorespiratory depression may occur if the paediatric dose regimen is applied *(see sections 4.2 and 4.4).*

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.

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

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 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.

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.

5.2 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.

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.

5.3 Preclinical safety 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 or alfentanil injection in plastic syringes *(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: 3 years.

Shelf-life of the product after first opening: Use immediately after opening. Any portion of the contents remaining after use should be discarded.

Shelf-life after dilution according to directions: When Diprivan is diluted with 0.5 % or 1 % Lidocaine injection (without preservatives) in plastic syringes, the resulting dilution must be used immediately.

After dilution with 5 % Dextrose Injection in PVC bags or glass infusion bottles or alfentanil injection (containing 500 micrograms/ml alfentanil) in plastic syringes, the shelf-life of the diluted product will be no greater than 6 hours when stored below 25 ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Unopened ampoules: 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 ampoules (20ml).
Pack size: 5 ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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. Diprivan and any syringe containing Diprivan are for single use in an individual patient. Any portion of the contents remaining after use should be discarded.

Asepsis for Diprivan and infusion equipment must be maintained *(see section 4.4 Special Warnings and Precautions for Use).*

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton
LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0970/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 06 November 2007

10 DATE OF REVISION OF THE TEXT

July 2009