November 16, 2009

Dear Healthcare Professional,

Due to the critical shortage of Propofol Injection in the United States market, APP is coordinating with the FDA to increase the availability of propofol products.

In conjunction with the FDA, and to alleviate shortages of this important medication, a decision has been made to allow the US market to be supplied with an international propofol 1% product, labeled as **Fresenius Propoven 1%** (propofol 1%). **Fresenius Propoven 1%** (propofol 1%) is manufactured in FDA inspected facilities by APP's parent company, Fresenius Kabi AG. All of these facilities are in compliance with FDA manufacturing standards.

Fresenius Propoven 1% (propofol 1%) contains the same active ingredient, propofol, in the same concentration as DIPRIVAN® (propofol 1%) and is a clinically acceptable substitute to other currently marketed generic propofol products in the US. **It is important to note that there are some key differences in the formulation and labeling between the US marketed propofol products and the international Fresenius Propoven 1% (propofol 1%), that you need to be aware of:**

- **Fresenius Propoven 1%** (propofol 1%) contains a combination of long-chain triglycerides (LCT), similar to those found in DIPRIVAN®; however, **Fresenius Propoven 1%** (propofol 1%) also contains medium-chain triglycerides (MCT) that are not present in the DIPRIVAN® formulation. As with DIPRIVAN® and other propofol products, special care should be applied in patients with disorders of fat metabolism, patients receiving Total Parentral Nutrition (TPN), and in patients with other conditions where lipid emulsions must be used with caution.
- **Fresenius Propoven 1%** (propofol 1%) does NOT contain an anti-microbial retardant such as ethylenediaminetetraacetic acid (EDTA), sodium meta-bisulfate, or benzyl alcohol/sodium benzoate.
    - **STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING.**
    - Each vial of **Fresenius Propoven 1%** (propofol 1%) is intended only for single administration for an individual patient. **Vials are not intended for multidose use.**
    - After being drawn up into a syringe, the syringe should be discarded after 6 hours. The unused portion of a vial should be discarded immediately following vial penetration.
    - As with any propofol 1% used for IV infusion, discard all product and infusion therapy systems after 12 hours.
- Although the **Fresenius Propoven 1%** (propofol 1%) label indicates that it may be used for general anesthesia in pediatric patients down to one month of age, it is recommended that, in keeping with the US propofol labels, **Fresenius Propoven 1%** (propofol 1%) be used for maintenance of anesthesia in patients above the age of two months. **Fresenius Propoven 1%** (propofol 1%) may be used for induction of anesthesia in patients above the age of 3 years.
- **Fresenius Propoven 1%** (propofol 1%) should not be used for sedation in patients less than 16 years of age.
- **Fresenius Propoven 1%** (propofol 1%) is contraindicated in patients who are allergic to soy or peanut.
- The barcode used on **Fresenius Propoven 1%** (propofol 1%) product is an international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the US. Institutions should confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being prepared and administered to individual patients.
- **Fresenius Propoven 1%** (propofol 1%) product information sheet contains a *patient information leaflet* as part of the international requirement for propofol 1%. For questions regarding **Fresenius Propoven 1%** (propofol 1%) in the US, please contact APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.

The product comparison table below also highlights the differences between DIPRIVAN® and **Fresenius Propoven 1%** (propofol 1%).

APP Pharmaceuticals
1501 East Woodfield Road
Suite 300 East
Schaumburg, IL 60173

Main 847-969-2700
Toll Free 888-391-6300
www.APPpharma.com

Please find attached a copy of the APP DIPRIVAN® & Fresenius Propoven 1% package insert.

To further supplement supply, APP continues to expedite manufacturing DIPRIVAN® to maintain weekly releases on all product presentations.

Please evaluate the use of **Fresenius Propoven** (propofol 1%) in your institution and begin placing orders immediately. If your institution is not willing to use **Fresenius Propoven** (propofol 1%), you may continue to order DIPRIVAN® and APP will continue to fill those orders through the allocation process. APP will reserve some DIPRIVAN® for those patients where **Fresenius Propoven** (propofol 1%) is contraindicated. Customers have the following options when ordering **Fresenius Propoven** (propofol 1%):

- Wholesalers can place drop ship orders on a customer's behalf directly with APP.
- Customers can order directly from APP by contacting Customer Service at 1-888-386-1300 between 7 a.m. – 6 p.m. Central Standard Time.

Until further notice, both **Fresenius Propoven** (propofol 1%) and DIPRIVAN® will remain on an allocation process. APP will be closely monitoring the distribution of DIPRIVAN® and **Fresenius Propoven 1%** (propofol 1%) to help manage continued imbalances in supply.

If you have additional questions, please contact Customer Service at 1-888-386-1300, Monday – Friday, between the hours of 7:00 a.m. and 6:00 p.m. (CST) or APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com. This communication and updated product information is available on the APP web site www.APPpharma.com as well as on the FDA Drug Shortage web site http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

To report adverse events among patients administered **Fresenius Propoven 1%** (propofol 1%), please call 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST). Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using FDA Form 3500 at http://www.fda.gov/medwatch/index.html.

We urge you to contact our Medical Information department at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com if you have any questions about the information contained in this letter or the safe and effective use of **Fresenius Propoven 1%** (propofol 1%).

Sincerely,

Arthur Pelletier
Vice President, Quality Assurance/Quality Control
APP Pharmaceuticals
A Company of the Fresenius Kabi Group

Enclosures:
1. *DIPRIVAN® Package Insert*
2. *Fresenius Propoven Package Insert*

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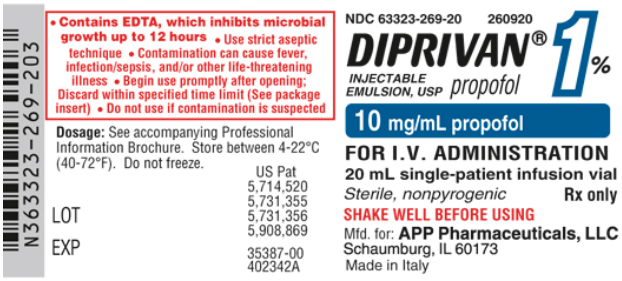
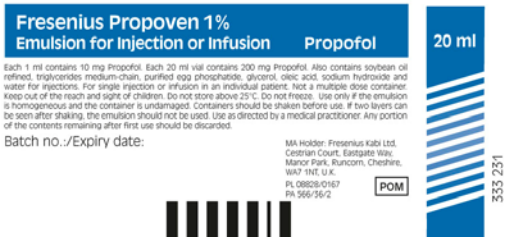
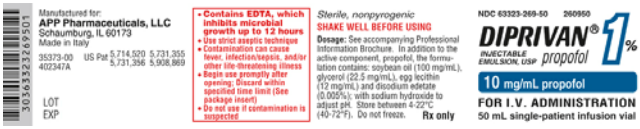
Comparison Table:

APP Label DIPRIVAN® (propofol 1%)	Fresenius Label Propoven 1% (propofol 1%)
	
	
	

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APP DIPRIVAN® (propofol 1%)	Fresenius Propoven 1% (propofol 1%)	What does this mean to you, as a Healthcare Professional?
Contains ethylenediaminetetraacetic acid (EDTA)	**Does not contain an anti-microbial retardant** such as ethylenediaminetetraacetic acid (EDTA), benzyl alcohol/sodium benzoate, or sodium meta-bisulfate	**Fresenius Propoven 1%** (propofol 1%) Fresenius **IS** a single dose vial for administration to a single patient. **Strict aseptic technique must always be maintained during handling**
Indications and contraindications: see package insert	Indications and contraindications: see package insert **Please note: see package insert on 4.2 method of administration, 4.3 contraindications, and 4.4 special warning and precautions for use**	Although the **Fresenius Propoven 1%** (propofol 1%) label indicates that it may be used for general anesthesia in pediatric patients down to one month of age, it is recommended that, in keeping with the US propofol labels, **Fresenius Propoven 1%** (propofol 1%) be used for maintenance of anesthesia in patients above the age of two months. **Fresenius Propoven 1%** (propofol 1%) may be used for induction of anesthesia in patients above the age of 3 years. **Fresenius Propoven 1%** (propofol 1%) should not be used for sedation in patients less than 16 years of age.
Contains long-chain triglycerides (LCT)	Contains a combination of medium-chain triglycerides (MCT) plus long-chain triglycerides (LCT)	The presence of MCTs should be taken into consideration when treating patients with disorders of fat metabolism or who are receiving TPN.
24-month expiration date	36-month expiration date	Extra 12-month expiry has no impact on safety or effectiveness.
Unit of use barcode on individual vials	No unit of use barcode	The barcode used on **Fresenius Propoven 1%** (propofol 1%) may not register accurately on US scanning systems. Other means of confirming the correct drug is being prepared and administered to the correct patient should be utilized.
N/A	Contains a *patient information leaflet*.	For questions **regarding Fresenius Propoven 1%** (propofol 1%) in the United States, please contact APP Medical Information at 1-800-551-7176 between the hours of 8 a.m. and 5 p.m. (CST), or e-mail appmedicalinfo@APPpharma.com.

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Fresenius Propoven 1%
Emulsion for Injection or Infusion
Propofol

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fresenius Propoven 1%, emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion contains 10 mg propofol.

Each 20 ml ampoule contains 200 mg propofol.
Each 20 ml vial contains 200 mg propofol.
Each 50 ml vial contains 500 mg propofol.
Each 100 ml vial contains 1000 mg propofol.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for injection or infusion
Isotonic, white oil-in-water emulsion

4. CLINICAL PARTICULAR

4.1 Therapeutic indications

Fresenius Propoven 1% is a short-acting intravenous general anaesthetic agent for

- induction and maintenance of general anaesthesia
- sedation of artificially ventilated patients in the Intensive Care Unit (ICU)
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia

4.2 Posology and method of administration

Fresenius Propoven 1% must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia or in the care of patients in intensive care.
Circulatory and respiratory functions should be constantly monitored (e.g. ECG, pulse oxymetry) and facilities for maintenance of patient airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.
For sedation during surgical and diagnostic procedures Fresenius Propoven 1% should not be administered by the same person conducting the surgical or diagnostic procedure.

The dose of Fresenius Propoven 1% emulsion should be individualised based on the response of the patient and premedications used.
Supplementary analgesic agents are generally required in addition to Fresenius Propoven 1%.

Posology

• General anaesthesia in adults:

Induction of anaesthesia:

For induction of anaesthesia Fresenius Propoven 1% should be titrated (approximately 20 - 40 mg propofol every 10 seconds) against the response of the patient until 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 propofol/kg body weight.

In patients over this age and in patients of ASA grades III and IV, especially those with impaired cardiac function, the requirements will generally be less and the total dose of Fresenius Propoven 1% may be reduced to a minimum of 1 mg propofol/kg body weight. Lower rates of administration of Fresenius Propoven 1% should be used (approximately 2 ml (20 mg propofol) every 10 seconds).

Maintenance of anaesthesia:

Anaesthesia can be maintained by administering Fresenius Propoven 1% either by continuous infusion or repeat bolus injections.

For maintenance of anaesthesia generally doses of 4 to 12 mg propofol/kg body weight/h should be given. A reduced maintenance dose of approximately 4 mg propofol/kg body weight/h may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

In elderly patients, patients in unstable general conditions, patients with impaired cardiac function or hypovolaemic patients and patients of ASA grades III and IV, the dosage of Fresenius Propoven 1% may be reduced further depending on the severity of the patient's condition and on the performed anaesthetic technique.

For maintenance of anaesthesia using repeat bolus injections dose increments of 25 to 50 mg propofol (= 2.5 - 5 ml Fresenius Propoven 1% should be given according to clinical requirements.

Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiopulmonary depression.

• General anaesthesia in children over 1 month of age:

Fresenius Propoven 1% is not advised for general anaesthesia in children younger than 1 month of age.

Induction of anaesthesia:

When used to induce anaesthesia, it is recommended that Fresenius Propoven 1% should be titrated slowly until the clinical signs show the onset of anaesthesia.

The dose should be adjusted for age and/or body weight.
Children over 8 years of age are likely to require approximately 2.5 mg propofol/kg body weight for induction of anaesthesia. Under this age the dose requirement may be higher. The initial dose should be 3 mg propofol/kg body weight. If necessary, additional doses in steps of 1 mg propofol/kg body weight can be administered.

Lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Administration of propofol by a Target Controlled Infusion (TCI) system is not advised for induction of general anaesthesia in children.

Maintenance of anaesthesia:

For maintenance of anaesthesia using continuous infusion doses of 9 to 15 mg propofol/kg body weight/h should be given.

Younger children, less than 3 years, may need higher dosage requirements, within the range of recommended dosages, when compared with older paediatric patients.

There is no data on maintenance of anaesthesia with repeated injections of propofol in children.

Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia.

A maximum duration of use of approximately 60 minutes should not be exceeded except where there is a specific indication for longer use e.g. malignant hyperthermia where volatile agents must be avoided.

Administration of propofol by a Target Controlled Infusion (TCI) system is not advised for maintenance of general anaesthesia in children.

• Sedation in adults during intensive care:

When used to provide sedation for ventilated patients under intensive care conditions, it is recommended that Fresenius Propoven 1% should be given by continuous infusion. The dose should be adjusted according to the depth of sedation required. Usually satisfactory sedation is achieved with administration rates in the range of 0.3 to 4.0 mg propofol/kg body weight/h. Rates of infusion greater than 4.0 mg propofol/kg body weight/h are not recommended (see section 4.4 Special warnings and precautions for use).

Propofol must not be used for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications).

Administration of Fresenius Propoven 1% by a Target Controlled Infusion (TCI) system is not advised for sedation in the Intensive Care Unit.

• Sedation for diagnostic and surgical procedures in adult patients:

To provide sedation during surgical and diagnostic procedures, doses and administration rates should be adjusted according to the clinical response. Most patients will require 0.5 - 1 mg propofol/kg body weight over 1 to 5 minutes for onset of sedation. Maintenance of sedation may be accomplished by titrating Fresenius Propoven 1% infusion to the desired level of sedation. Most patients will require 1.5 - 4.5 mg propofol/kg body weight/h. The infusion may be supplemented by bolus administration of 10 – 20 mg (1 – 2 ml Fresenius Propoven 1% if a rapid increase of the depth of sedation is required.

In patients older than 55 years and in patients of ASA grades III and IV lower doses of Fresenius Propoven 1% may be required and the rate of administration may need to be reduced.

Propofol must not be used for sedation for diagnostic and surgical procedures in patients of 16 years of age or younger.

Method of administration

For intravenous use.

Fresenius Propoven 1% can be used for infusion undiluted or diluted with Dextrose 5% intravenous infusion solution or Sodium chloride 0.9% intravenous infusion solution only, in glass infusion bottles.

Containers should be shaken before use.
Use only homogeneous preparations and undamaged containers.

Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

Fresenius Propoven 1% is a lipid containing emulsion without antimicrobial preservatives and may support rapid growth of microorganisms.

The emulsion 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 Fresenius Propoven 1% and infusion equipment throughout the infusion period. Co-administration of other medicinal products or fluids added to the Fresenius Propoven 1% infusion line must occur close to the cannula site using a Y-piece connector or a three-way valve.

Fresenius Propoven 1% must not be mixed with other solutions for infusion or injection. But 5% w/v glucose solution, 0.9% w/v sodium chloride solution or 0.18% w/v sodium chloride and 4% w/v glucose solution may be administered via suitable appendages at the cannula site.
Fresenius Propoven 1% must not be administered via a microbiological filter.

Fresenius Propoven 1% and any infusion equipment containing Fresenius Propoven 1% are for **single** administration in an **individual** patient. After use remaining solution of Fresenius Propoven 1% (10 mg/1 ml) MCT Fresenius has to be discarded.

Infusion of undiluted Fresenius Propoven 1%:

When Fresenius Propoven 1% is infused undiluted, it is recommended that equipment such as burettes, drop counter, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

As usual for fat emulsions, the infusion of Fresenius Propoven 1%, via **one** infusion system must not exceed 12 hours. After 12 hours, the infusion system and reservoir of Fresenius Propoven 1% must be discarded or replaced if necessary.

Infusion of diluted Fresenius Propoven 1%:

For administering infusion of diluted Fresenius Propoven 1%, burettes, drop counters or volumetric infusion pumps should always be used to control infusion rates and to avoid the risk of accidentally uncontrolled infusion of large volumes of diluted Fresenius Propoven 1%. This risk has to be taken into account when the decision for the maximum dilution in the burette is made.

The maximum dilution must not exceed 1 part of Fresenius Propoven 1% with 4 parts of 5% w/v glucose solution or 0.9% w/v sodium chloride solution (minimum concentration 2 mg propofol/ml). The mixture should be prepared aseptically (controlled and validated conditions preserved) immediately prior to administration and must be administered within 6 hours after preparation.

Fresenius Propoven 1% must not be mixed with other solutions for infusion or injection. However co-administration of a 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 0.18% w/v sodium chloride and 4% w/v glucose solution with Fresenius Propoven 1% is permitted via a Y-piece connector close to the injection site.

To reduce pain on the injection site, lidocaine may be injected immediately before the use of Fresenius Propoven 1% or Fresenius Propoven 1% may be mixed, immediately for use, with preservative free lidocaine injection (20 parts of Fresenius Propoven 1% with up to 1 part of 1% lidocaine injection solution) under controlled and validated aseptical conditions. The mixture has to be administered within 6 hours after preparation.

Muscle relaxants like atracurium and mivacurium should only be administered after flush of the same infusion site used for Fresenius Propoven 1%.

Duration of administration

The duration of administration must not exceed 7 days.

4.3 Contraindications

Fresenius Propoven 1% must not be used

- in patients with a known hypersensitivity to propofol or to any of the excipients of the emulsion
- in patients who are allergic to soya or peanut
- for sedation in children 16 years of age and younger (see section 4.4 Special warnings and precautions for use)

4.4 Special warning and precautions for use

In patients with cardiac, respiratory, renal or hepatic impairment or in elderly, debilitated, hypovolaemic or epileptic patients or patients with disorders of consciousness Fresenius Propoven 1% should be administered with caution and a reduced administration rate (see section 4.2 Posology and method of administration).

Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of Fresenius Propoven 1%.

Before anaesthesia of an epileptic patient, it should be checked that the patient has received the antiepileptic treatment. Although several studies have demonstrated efficacy in treating status epilepticus, administration of propofol in epileptic patients may also increase the risk of seizure.

Fresenius Propoven 1% should not be administered in patients with advanced cardiac failure or other severe myocardial disease except with extreme caution and intensive monitoring.

The risk of relative vagotonia may be increased because propofol lacks vagolytic activity. It 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 Fresenius Propoven 1% is used in conjunction with other agents likely to cause a bradycardia.

Use is not recommended with electroconvulsive therapy.

As with other sedative agents, when propofol 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.

Special care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used with caution. If patients receive parenteral nutrition it is necessary to take account of the amount of lipid infusion as part of the Fresenius Propoven 1% formulation: 1.0 ml Fresenius Propoven 1% contains 0.1 gram of fat.

Lipids should be monitored in the Intensive Care Unit treatment after 3 days.

Due to a higher dosage in patients with severe overweight the risk of haemodynamic effects on the cardiovascular system should be taken into consideration.
Special care should be recognised in patients with a high intracranial pressure and a low mean arterial pressure as there is a risk of a significant decrease of the intracerebral perfusion pressure.

To reduce pain on the injection site during induction of anaesthesia with Fresenius Propoven 1%, lidocaine can be injected prior to the propofol emulsion.

Dilutions with lidocaine solution must not be used in patients with hereditary acute porphyria.

Propofol is not advised for general anaesthesia in children younger than 1 month of age. The safety of propofol 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 propofol/kg body weight/h.

Patient Information Leaflet

Fresenius Propoven 1%
Emulsion for Injection or Infusion
Propofol

What you should know about Propofol

- Keep this leaflet with you while you are receiving Propofol. You may want to read it later.
- Please read this leaflet carefully as it contains a summary of information about your medicine.
- If you are not sure about anything, please ask your doctor, hospital pharmacist or a member of the nursing staff.
- Propofol can only be prescribed by a doctor, who will be trained in anaesthesia or in the care of patents in intensive care.

What is in your medicine?

Propofol is a milky white liquid, containing 10 mg Propofol in each millilitre. It is supplied in either 20 ml sealed glass ampoules or 20 ml, 50 ml or 100 ml glass vials.
The product also contains the following inactive ingredients soybean oil refined, triglycerides medium chain, purified egg phosphatide, glycerol, oleic acid, sodium hydroxide and water for injections.
Propofol belongs to a group of medicines called general anaesthetics. This means that it causes you to become unconscious (asleep) whilst surgical operations and other procedures are being conducted. It can also be used in some circumstances to sedate you (make you feel sleepy without sending you to sleep).

Who has made your medicine?

The marketing authorisation holder is Fresenius Kabi Limited, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire, WA7 1NT, U.K.
Fresenius Propoven 1% is manufactured on behalf of Fresenius Kabi Ltd. by Fresenius Kabi Austria GmbH, Hafnerstrasse 36, A-8055 Graz, Austria and Fresenius Kabi AB, Rapsgatan 7, S-75174 Uppsala, Sweden.

What is your medicine for?

Propofol is used either to make you unconscious (asleep) or to sedate you (make you sleepy), while you are having an operation or other procedures are being conducted or you are undergoing intensive care.

When should Propofol not be used.

You should not be given Propofol if:
- You have ever received Propofol before and have experienced an allergic reaction to it or to any of the inactive ingredients
- You are allergic to soya or peanuts.

Propofol must not be used for sedation in children 16 years of age and younger.

What precautions should be taken with Fresenius Propoven 1%?

If any of the following apply, propofol may not be suitable for you or your doctor may need to take special precautions if:

- You have problems with your heart, breathing, kidneys or liver.
- Your blood pressure is to high or to low.
- You have epilepsy
- You have been told that you have very high fat levels in your blood or your body has problems being able to handle and use fat.
- You have had a stroke or a head injury
- You have a rare condition called hereditary acute porphyria.
- You are elderly or debilitated, or severely overweight
- You are pregnant or think that you may be pregnant, or are breast-feeding.

Before receiving propofol tell you doctor if you think any of these may apply to you.

You should be sure that your doctor is aware if you are taking any other medicines, including any that don't require a prescription. Propofol can react badly with some other medicines.

After receiving Propofol your ability to drive a car or operate machinery may be affected for some time. Therefore, if you are able to go home shortly after receiving propofol you should avoid alcohol and not drive a car. Your doctor should not let you go home unaccompanied. Ask your doctor when you can return to work, particularly if you use machinery or heavy equipment.

Receiving your medicine

Propofol will be given by, or under the direct supervision of, your anaesthetist or intensive care doctor, who will closely control the amount of Propofol given to you. Dosage will be adjusted to the individual's requirements so that adequate anaesthesia or sedation is obtained. The dose of Propofol you require may vary according to other medicines, including premedications that you have received, and on your age, size, and the level of sleepiness required. Your condition will be continuously monitored and your doctor may need to use several different medicines to keep you asleep or sedated.

For induction of anaesthesia most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/propofol/kg body weight. For maintenance of anaesthesia generally doses of 4 to 12 mg /propofol/kg body weight/h are given.

For sedation of adults during intensive care the dose should be adjusted according to the depth of sedation required. Using continuous infusion doses of 0.3 to 4.0 mg/propofol/kg body weight/h are typically given. Rates of infusion greater than 4.0 mg/propofol/kg body weight/h are not recommended.

This exceeds the maximum dosage of 4 mg propofol/kg body weight/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with increased intracranial pressure (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 propofol/kg body weight/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the propofol 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.

Special care should be exercised when propofol is used for anaesthesia in infants and children up to 3 years of age, although currently available data do not suggest significant differences in terms of safety compared with children older than 3 years.

In isolated cases there may be a phase of postoperative unconsciousness that may be accompanied by an increased muscle tone. The occurrence of such an event is not related to whether the patient was awake or not. Although consciousness returns spontaneously, unconscious patients should be kept under close observation.
Fresenius Propoven 1% contains soybean oil, which might cause severe allergic reaction in rare cases.

Full recovery from general anaesthesia should be confirmed prior to discharge.

4.5 Interaction with other medicinal products and other forms of interaction

Fresenius Propoven 1% can be used in combination with other medicinal products for anaesthesia (premedications, volatile anaesthetics, analgesics, muscle relaxants, local anaesthetics).
Severe interactions with these medicinal products have been reported. Some of these centrally acting medicinal products may exhibit a circulatory and respiratory depressive effect, thus leading to increased effects when used together with Fresenius Propoven 1%.

Lower doses may be required when general anaesthesia is carried out in conjunction with regional anaesthesia.

Concomitant use of benzodiazepines, parasympatholytic agents or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

After additional premedication with opioids, the sedative effects of propofol may be intensified and prolonged, and there may be a higher incidence and longer duration of apnoea.

It should be taken into consideration that concomitant use of propofol and medicinal products for premedication, inhalation agents, or analgesic agents may potentiate anaesthesia and cardiovascular side effects.
Concomitant use of central nervous system depressants (e.g. alcohol, general anaesthetics, narcotic analgesics) will result in intensification of their sedative effects. When Fresenius Propoven 1% is combined with centrally depressant agents administered parenterally, severe respiratory and cardiovascular depression may occur.

After administration of fentanyl, the blood level of propofol may be temporarily increased with an increase in the rate of apnoea.

Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmin.
Leucoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving cyclosporine.

4.6 Pregnancy and lactation

The safety of propofol during pregnancy has not been established. Therefore, propofol should not be used in pregnant women unless clearly necessary. Propofol crosses the placenta and may be associated with neonatal depression (see also section 5.3 Preclinical safety data). High doses (more than 2.5 mg propofol/kg body weight for induction or 6 mg propofol/kg body weight/h for maintenance of anaesthesia) should be avoided.

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

After administration of Fresenius Propoven 1%, the patient should be kept under observation for an appropriate period of time. The patient should be instructed not to drive, operate machinery, or work in potentially hazardous situations. The patient should not be allowed to go home unaccompanied, and should be instructed to avoid consumption of alcohol.

4.8 Undesirable effects

Commonly observed side effects of propofol are hypotension and respiratory depression. These effects depend on the propofol dose administered but also on the type of premedication and other concomitant medication. Specifically, the following side effects have been observed:

Immune system disorders:
Rare (< 1:1000, ≥ 1:10 000):
Clinical features of anaphylaxis, which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Psychiatric disorders:
Rare (< 1:1000, ≥ 1:10 000):
Euphoria and sexual disinhibition during the recovery period.

Nervous system disorders:
Common (< 1:10, ≥ 1:100):
During induction of anaesthesia spontaneous movements and myocloni, minimal excitation.

Rare (< 1:1000, ≥ 1:10 000):
Headache, vertigo, shivering and sensations of cold during the recovery period.
Epileptiform movements including convulsions and opisthotonus.

Very rare (< 1:10 000):
Delayed epileptiform attacks, the delay period ranging from a few hours to several days.
Risk of convulsions in epileptic patients after administration of propofol.
Cases of postoperative unconsciousness (see section 4.4 Special warnings and precautions for use).

Cardiac disorders / Vascular disorders:
Common (< 1:10, ≥ 1:100):
During induction of anaesthesia, hypotension, bradycardia, tachycardia, hot flushes.

Uncommon (< 1:100, ≥ 1:1000):
Marked hypotension. This may require a lowering of the administration rate of Fresenius Propoven 1% and/or fluid replacement therapy, if necessary vasoconstrictive medicinal products. Account should be taken of the possibility of a severe drop in blood pressure in patients with impaired coronary or cerebral perfusion or those with hypovolaemia.
Bradycardia during general anaesthesia with progressive severity (asystole). The intravenous administration of an anticholinergic medicinal product prior to induction or during maintenance of anaesthesia should be considered (see also section 4.4. Special warnings and precautions for use).

Rare (< 1:1000, ≥ 1:10 000):
Arrhythmia during the recovery period.
Thrombosis and phlebitis.

Respiratory, thoracic and mediastinal disorders:
Common (< 1:10, ≥ 1:100):
During induction of anaesthesia hyperventilation, transient apnoea, coughing, singultus.

Uncommon (< 1:100, ≥ 1:1000):
Coughing during maintenance of anaesthesia.

Rare (< 1:1000, ≥ 1:10 000):
Coughing during the recovery period.

Very rare (< 1:10 000):
Pulmonary oedema.

Gastrointestinal disorders:
Rare (< 1:1000, ≥ 1:10 000):
Nausea or vomiting during the recovery period.

Very rare (< 1:10 000):
Pancreatitis has been reported after administration of propofol. A causal relationship, however, could not be established.

Skin and subcutaneous tissue disorders:
Very rare (< 1:10 000):
Severe tissue responses after accidental paravenous application.

Renal and urinary disorders:
Rare (< 1:1000, ≥ 1:10 000):
Cases of discoloration of urine following prolonged administration of propofol.

General disorders and administration site conditions:
Very common (> 1:10):
Local pain occurring during the initial injection. Prophylaxis or treatment see below.

The local pain which may occur during the initial injection of Fresenius Propoven 1% can be minimised by the co-administration of lidocaine (see section 4.2 Method of administration, section "Infusion of diluted Fresenius Propoven 1% and by injection or infusion into the larger veins of the forearm and antecubital fossa. Upon co-administration of lidocaine the following undesirable effects may occur rarely (< 1:1000, ≥ 1:10 000): giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock.

Rare (< 1:1000, ≥ 1:10 000):
Cases of post-operative fever

Very rare (< 1:10 000):
There have been reports of isolated cases of severe undesirable effects presenting as a complex of symptoms including: rhabdomyolysis, metabolic acidosis, hyperkalaemia, and cardiac failure, sometimes with fatal outcome. Most of these effects have been observed in patients in intensive care with doses exceeding 4 mg/kg body weight/h. For more detail, see section 4.4 Special warnings and precautions for use.

4.9 Overdose

Overdose is likely to cause cardiovascular and respiratory depression. Respiratory depression is treated with artificial ventilation. Cardiovascular depression may require lowering the patient's head and administering plasma volume substitutes and vasopressive agents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics
ATC-Code: NO1AX10

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 – 6 minutes).

With the recommended dosage schedule, a clinically relevant accumulation of propofol after repeated bolus injection or after infusion has not been observed. Patients recover consciousness rapidly.

Bradycardia and hypotension occasionally occur during induction of anaesthesia probably due to a lack of vagolytic activity. The cardio-circulatory situation usually normalises during maintenance of anaesthesia.

5.2 Pharmacokinetic properties

After intravenous administration about 98 % of propofol is bound to plasma protein.

After intravenous bolus administration the initial blood level of propofol declines rapidly due to rapid distribution into different compartments (α-phase). The distribution half-life has been calculated as 2 – 4 minutes.
During elimination the decline of blood levels is slower. The elimination half-life during the β-phase is in the range of 30 to 60 minutes. Subsequently a third deep compartment becomes apparent, representing the re-distribution of propofol from weakly perfused tissue.

Clearance is higher in children compared with adults.

The central volume of distribution is in the range of 0.2 – 0.79 l/kg body weight, the steady-state volume of distribution in the range of 1.8 – 5.3 l/kg body weight. Propofol is rapidly cleared from the body (total clearance 1.5 to 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form glucuronides of propofol and glucuronides and sulphate conjugates of its corresponding quinol. All metabolites are inactive. About 88 % of an administered dose is excreted in the form of metabolites in urine. Only 0.3 % of the administered dose is excreted unchanged in urine.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on repeated dose toxicity or genotoxicity.

Carcinogenicity studies have not been conducted. Reproductive toxicity studies have shown effects related to pharmacodynamic properties of propofol only at high doses. Teratogenic effects have not been observed.
In local tolerance studies, intramuscular injection resulted in tissue damage around the injection site.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya-bean oil, refined
Triglycerides medium-chain
Purified egg phosphatides
Glycerol
Oleic acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The shelf life of the medicinal product in its original package is 3 years.

The infusion of undiluted Fresenius Propoven 1% via one infusion system must not exceed 12 hours.
Dilutions with 5% w/v glucose solution or 0,9% w/v sodium chloride solution or an admixture 1% lidocaine injection solution (at least 2 mg propofol per ml) should be prepared aseptically (controlled and validated conditions preserved) immediately before administration and must be administered within 6 hours after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.

6.5 Nature and contents of container

Colourless glass ampoule (type I) of 20 ml, packs of 5 units
Colourless glass vial (type I or II) of 20 ml with a bromobutyl rubber closure, packs of 1 unit and 5 and 10 units

Colourless glass vial (type II) of 50 ml with a bromobutyl rubber closure, packs of 1 unit and 10 and 15 units
Colourless glass vial (type II) of 100 ml with a bromobutyl rubber closure, packs of 1 unit and 10 and 15 units

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Fresenius Propoven 1% should not be mixed prior to administration with injection or infusion solutions other than 5% w/v glucose solution or 0.9% w/v sodium chloride solution or 1% lidocaine injection solution (see also section 4.2 Posology and method of administration). Final propofol concentration must not be below 2 mg/ml.

For single use. Any unused emulsion must be discarded.

Containers should be shaken before use.
If two layers can be seen after shaking the emulsion should not be used.
Use only homogeneous preparations and undamaged containers.

Prior to use, the ampoule neck or rubber membrane should be cleaned using an alcohol spray or a swab dipped in alcohol. After use, tapped containers must be discarded.

7. MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited,
Cestrian Court, Eastgate Way, Manor Park,
Runcorn, Cheshire, WA7 1NT, U.K.

8. MARKETING AUTHORISATION NUMBER

PL 08828/0167 UK
PA 566/36/1-2 Ireland

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/4/05 Ireland
8/6/05 UK

10. DATE OF REVISION OF THE TEXT

November 2006

For sedation for diagnostic and surgical procedures in adults generally doses of 0.5 to 1 mg /propofol/kg body weight over 1 to 5 minutes are required for onset of sedation. Maintenance of sedation will require 1.5 – 4.5 mg /propofol/kg body weight/h.

Dose requirements may be higher for children and lower for elderly patients.

Reduced doses may be sufficient during less stressful surgical procedures such as minimal invasive surgery.

Your medicine will be given to you as an injection into a vein, usually in the back of the hand or in the forearm through a needle, or a fine plastic tube called a cannula.

For maintenance of anaesthesia or sedation, your medicine may be given as an intravenous infusion (or IV drip) using an electric pump which will automatically control the rate at which the infusion is given.

What undesirable events may be associated with this medicine

As with all medicines, propofol can cause undesirable side effects:

Very common (occurring in more than 10% of patients)

The initial injection of Propofol may cause some local discomfort or pain while the injection is given.

Common (occurring between one in ten and one in a hundred patients).

As with other anaesthetic agents, you may have a fall in your blood pressure, an increase or decrease in the rate of your heart, hot flushes, changes in your breathing pattern, coughing and hiccups. Your doctor can deal with these if they happen.
During induction of anaesthesia muscular spasms and excitation may be observed. These do not normally cause any problems.

Uncommon (occurring between one in a hundred and one in a thousand patients)

Uncommonly patients have a significant fall in blood pressure or slowing of the heart rate, requiring intervention by the anaesthetist.
Coughing during maintenance of anaesthesia is reported uncommonly.

Rare (occurring between one in a thousand and one in ten thousand patients)

Severe allergic reactions (e.g. swelling of the throat, difficulty breathing, reddening of the skin or low blood pressure).
Redness or soreness or a blood clot in the vein where the propofol was injected.
During the recovery period coughing, being sick or feeling sick, headache, vertigo, shivering or feeling cold, fever, epileptic movements or spasms, irregular heartbeat, euphoria and sexual disinhibition are reported rarely.
Discolouration of urine may occur rarely following prolonged administration of propofol.

Very rare (occurring in less than one in ten thousand patients)

There have been very rare reports of:
Inflammation of the pancreas (pancreatitis)
Too much fluid in the lungs.
Post-operative unconsciousness have also been observed.
Delayed epileptic convulsions (fits).
Severe tissue damage after accidental misplacement of the injection outside the vein.

Muscle damage has been reported very rarely, resulting in too much acid or too much potassium in your blood, and very rarely heart failure. Most of these severe reactions have followed prolonged administration during Intensive Care.

Do not be alarmed by this list of possible events. You may not have any of them. But if you think you experience any side effects please tell your doctor or nursing staff immediately.

What should be done in case of overdose

Your doctor will ensure that you receive the right amount of propofol for you and for the procedure you are undergoing. However different people need different doses and if you do receive too much for you, your anaesthetist may need to take measures to make sure your heart and breathing are adequately supported. This is why anaesthetic drugs are only administered by doctors trained in anaesthesia or in the care of patents in intensive care

Storing Propofol

The shelf life if the product in its original package is 3 years.
It should not be used after the expiry date shown on the container label.
Containers should be shaken before use.
If two layers can be seen after shaking, the emulsion should not be used.
Use only homogeneous preparations in undamaged containers. Do not store above 25°C. Do not freeze.
Keep out of the reach and sight of children.
For single use. Any unused emulsion must be discarded
Your doctor and hospital pharmacist are responsible for the correct storage, use and disposal of Propofol

Date of Preparation: February 2007.

Fresenius Kabi

DIPRIVAN®
(propofol) **INJECTABLE EMULSION, USP** **1%**

10 mg/mL propofol

FOR IV ADMINISTRATION

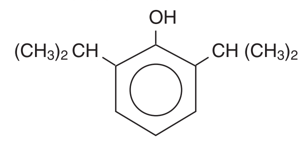
451094A
Revised: July 2009
35375-02

F.P.O.

Rx only

Strict aseptic technique must always be maintained during handling. Diprivan Injectable Emulsion is a single-use parenteral product which contains 0.005% disodium edetate to inhibit the rate of growth of microorganisms, for up to 12 hours, in the event of accidental extrinsic contamination. However, Diprivan Injectable Emulsion can still support the growth of microorganisms, as it is not an antimicrobially preserved product under USP standards. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see DOSAGE AND ADMINISTRATION, *Handling Procedures*). There have been reports in which failure to use aseptic technique when handling Diprivan Injectable Emulsion was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

DESCRIPTION:
DIPRIVAN® (propofol) Injectable Emulsion, USP is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol. The structural formula is:



$C_{12}H_{18}O$ M.W. 178.27

Propofol is slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL); and disodium edetate (0.005%); with sodium hydroxide to adjust pH. The DIPRIVAN Injectable Emulsion, USP is isotonic and has a pH of 7 to 8.5.

CLINICAL PHARMACOLOGY:

General

DIPRIVAN Injectable Emulsion is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol induces hypnosis, with minimal excitation, usually within 40 seconds from the start of injection (the time for one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, accounting for the rate of induction of anesthesia. The mechanism of action, like all general anesthetics, is poorly understood. However, propofol is thought to produce its sedative/anesthetic effects by the positive mondulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors.

Pharmacodynamics

Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. Steady-state propofol blood concentrations are generally proportional to infusion rates. Undesirable side effects, such as cardiorespiratory depression, are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in infusion rates. An adequate interval (3 to 5 minutes) must be allowed between dose adjustments in order to assess clinical effects.

The hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effect is arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), there is an increase in the incidence and the degree of depression of cardiac output. Addition of an opioid, used as a premedicant, further decreases cardiac output and respiratory drive.

If anesthesia is continued by infusion of DIPRIVAN Injectable Emulsion, the stimulation of endotracheal intubation and surgery may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN Injectable Emulsion during induction of anesthesia are generally more pronounced than with other intravenous (IV) induction agents.

Induction of anesthesia with DIPRIVAN Injectable Emulsion is frequently associated with apnea in both adults and pediatric patients. In adult patients who received DIPRIVAN Injectable Emulsion (2 to 2.5 mg/kg), apnea lasted less than 30 seconds in 7% of patients, 30 to 60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In pediatric patients from birth through 16 years of age assessable for apnea who received bolus doses of DIPRIVAN Injectable Emulsion (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30 to 60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

During maintenance of general anesthesia, DIPRIVAN Injectable Emulsion causes a decrease in spontaneous minute ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and concurrent use of other medications (e.g., opioids, sedatives, etc.).

During monitored anesthesia care (MAC) sedation, attention must be given to the cardiorespiratory effects of DIPRIVAN Injectable Emulsion. Hypotension, oxyhemoglobin desaturation, apnea, and airway obstruction can occur, especially following a rapid bolus of DIPRIVAN Injectable Emulsion. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus administration in order to minimize undesirable cardiorespiratory effects. In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**).

Clinical and preclinical studies suggest that DIPRIVAN Injectable Emulsion is rarely associated with elevation of plasma histamine levels.

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injectable Emulsion produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic vascular resistance.

Clinical studies indicate that DIPRIVAN Injectable Emulsion when used in combination with hypocarbia increases cerebrovascular resistance and decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure. DIPRIVAN Injectable Emulsion does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension (see ***Clinical Trials***, **Neuroanesthesia**).

Clinical studies indicate that DIPRIVAN Injectable Emulsion does not suppress the adrenal response to ACTH.

Animal studies and limited experience in susceptible patients have not indicated any propensity of DIPRIVAN Injectable Emulsion to induce malignant hyperthermia.

Hemosiderin deposits have been observed in the livers of dogs receiving DIPRIVAN Injectable Emulsion containing 0.005% disodium edetate over a four-week period; the clinical significance of this is unknown.

Pharmacokinetics

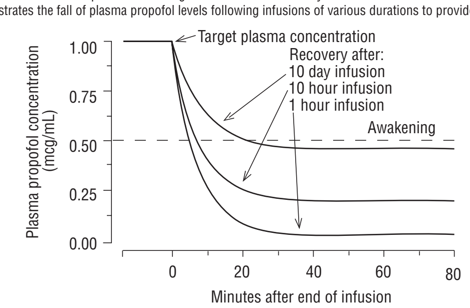
The pharmacokinetics of propofol are well described by a three compartment linear model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues.

Following an IV bolus dose, there is rapid equilibration between the plasma and the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. Distribution accounts for about half of this decline following a bolus of propofol. However, distribution is not constant over time, but decreases as body tissues equilibrate with plasma and become saturated. The rate at which equilibration occurs is a function of the rate and duration of the infusion. When equilibration occurs there is no longer a net transfer of propofol between tissues and plasma.

Discontinuation of the recommended doses of DIPRIVAN Injectable Emulsion after the maintenance of anesthesia for approximately one hour, or for sedation in the ICU for one day, results in a prompt decrease in blood propofol concentrations and rapid awakening. Longer infusions (10 days of ICU sedation) result in accumulation of significant tissue stores of propofol, such that the reduction in circulating propofol is slowed and the time to awakening is increased.

By daily titration of DIPRIVAN Injectable Emulsion dosage to achieve only the minimum effective therapeutic concentration, rapid awakening within 10 to 15 minutes can occur even after long-term administration. If, however, higher than necessary infusion levels have been maintained for a long time, propofol redistribution from fat and muscle to the plasma can be significant and slow recovery.

The figure below illustrates the fall of plasma propofol levels following infusions of various durations to provide ICU sedation.



The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions a reduction in the infusion rate is appropriate by as much as half the initial infusion rate in order to maintain a constant plasma level. Therefore, failure to reduce the infusion rate in patients receiving DIPRIVAN Injectable Emulsion for extended periods may result in excessively high blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN Injectable Emulsion infusion for ICU sedation.

Adults

Propofol clearance ranges from 23 to 50 mL/kg/min (1.6 to 3.4 L/min in 70 kg adults). It is chiefly eliminated by hepatic conjugation to inactive metabolites which are excreted by the kidney. A glucuronide conjugate accounts for about 50% of the administered dose. Propofol has a steady-state volume of distribution (10-day infusion) approaching 60 L/kg in healthy adults. A difference in pharmacokinetics due to gender has not been observed. The terminal half-life of propofol after a 10-day infusion is 1 to 3 days.

Geriatrics

With increasing patient age, the dose of propofol needed to achieve a defined anesthetic end point (dose-requirement) decreases. This does not appear to be an age-related change in pharmacodynamics or brain sensitivity, as measured by EEG burst suppression. With increasing patient age, pharmacokinetic changes are such that, for a given IV bolus dose, higher peak plasma concentrations occur, which can explain the decreased dose requirement. These higher peak plasma concentrations in the elderly can predispose patients to cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or arterial oxygen desaturation. The higher plasma levels reflect an age-related decrease in volume of distribution and intercompartmental clearance. Lower doses are therefore recommended for initiation and maintenance of sedation and anesthesia in elderly patients (see **DOSAGE AND ADMINISTRATION**).

Pediatrics

The pharmacokinetics of propofol were studied in children between 3 and 12 years of age who received DIPRIVAN Injectable Emulsion for periods of approximately 1 to 2 hours. The observed distribution and clearance of propofol in these children were similar to adults.

Organ Failure

The pharmacokinetics of propofol do not appear to be different in people with chronic hepatic cirrhosis or chronic renal impairment compared to adults with normal hepatic and renal function. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.

Clinical Trials

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

Pediatric Anesthesia

DIPRIVAN Injectable Emulsion was studied in clinical trials which included cardiac surgical patients. Most patients were 3 years of age or older. The majority of the patients were healthy ASA-PS I or II patients. The range of doses in these studies are described in Tables 1 and 2.

TABLE 1. PEDIATRIC INDUCTION OF ANESTHESIA

Age Range	**Induction Dose** Median (range)	**Injection Duration** Median (range)
Birth through 16 years	2.5 mg/kg (1 to 3.6)	20 sec. (6 to 45)

TABLE 2. PEDIATRIC MAINTENANCE OF ANESTHESIA

Age Range	**Maintenance Dosage** (mcg/kg/min)	**Duration** (minutes)
2 months to 2 years	199 (82 to 394)	65 (12 to 282)
2 to 12 years	188 (12 to 1041)	69 (23 to 374)
>12 through 16 years	161 (84 to 359)	69 (26 to 251)

Neuroanesthesia

DIPRIVAN Injectable Emulsion was studied in patients undergoing craniotomy for supratentorial tumors in two clinical trials. The mean lesion size (anterior/posterior x lateral) was 31 mm x 32 mm in one trial and 55 mm x 42 mm in the other trial respectively. Anesthesia was induced with a median Diprivan dose of 1.4 mg/kg (range: 0.9 to 6.9 mg/kg) and maintained with a median maintenance Diprivan dose of 146 mcg/kg/min (range: 68 to 425 mcg/kg/min). The median duration of the Diprivan maintenance infusion was 285 minutes (range: 48 to 622 minutes).

DIPRIVAN Injectable Emulsion was administered by infusion in a controlled clinical trial to evaluate its effect on cerebrospinal fluid pressure (CSFP). The mean arterial pressure was maintained relatively constant over 25 minutes with a change from baseline of -4% ± 17% (mean ± SD). The change in CSFP was -46% ± 14%. As CSFP is an indirect measure of intracranial pressure (ICP), DIPRIVAN Injectable Emulsion, when given by infusion or slow bolus in combination with hypocarbia, is capable of decreasing ICP independent of changes in arterial pressure.

Intensive Care Unit (ICU) Sedation

Adult Patients

DIPRIVAN Injectable Emulsion was compared to benzodiazepines and opioids in clinical trials involving ICU patients. Of these, 302 received DIPRIVAN Injectable Emulsion and comprise the overall safety database for ICU sedation.

Across all clinical studies, the mean infusion maintenance rate for all DIPRIVAN Injectable Emulsion patients was 27 ± 21 mcg/kg/min. The maintenance infusion rates required to maintain adequate sedation ranged from 2.8 mcg/kg/min to 130 mcg/kg/min. The infusion rate was lower in patients over 55 years of age (approximately 20 mcg/kg/min) compared to patients under 55 years of age (approximately 38 mcg/kg/min). Although there are reports of reduced analgesic requirements, most patients received opioids for analgesia during maintenance of ICU sedation. In these studies, morphine or fentanyl was used as needed for analgesia. Some patients also received benzodiazepines and/or neuromuscular blocking agents. During long-term maintenance of sedation, some ICU patients were awakened once or twice every 24 hours for assessment of neurologic or respiratory function.

In Medical and Postsurgical ICU studies comparing DIPRIVAN Injectable Emulsion to benzodiazepine infusion or bolus, there were no apparent differences in maintenance of adequate sedation, mean arterial pressure, or laboratory findings. Like the comparators, DIPRIVAN Injectable Emulsion reduced blood cortisol during sedation while maintaining responsivity to challenges with adrenocorticotropic hormone (ACTH). Case reports from the published literature generally reflect that DIPRIVAN Injectable Emulsion has been used safely in patients with a history of porphyria or malignant hyperthermia.

In hemodynamically stable head trauma patients ranging in age from 19 to 43 years, adequate sedation was maintained with DIPRIVAN Injectable Emulsion or morphine. There were no apparent differences in adequacy of sedation, intracranial pressure, cerebral perfusion pressure, or neurologic recovery between the treatment groups. In literature reports of severely head-injured patients in Neurosurgical ICUs, DIPRIVAN Injectable Emulsion infusion and hyperventilation, both with and without diuretics, controlled intracranial pressure while maintaining cerebral perfusion pressure. In some patients, bolus doses resulted in decreased blood pressure and compromised cerebral perfusion pressure.

DIPRIVAN Injectable Emulsion was found to be effective in status epilepticus which was refractory to the standard anticonvulsant therapies. For these patients, as well as for ARDS/respiratory failure and tetanus patients, sedation maintenance dosages were generally higher than those for other critically ill patient populations.

Pediatric Patients

A single, randomized, controlled, clinical trial that evaluated the safety and effectiveness of DIPRIVAN versus standard sedative agents (SSA) was conducted on 327 pediatric ICU patients. Patients were randomized to receive either DIPRIVAN 2%, (113 patients), DIPRIVAN 1%, (109 patients), or an SSA (eg, lorazepam, chloral hydrate, fentanyl, ketamine, morphine, or phenobarbital). DIPRIVAN therapy was initiated at an infusion rate of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a standardized level. The results of the study showed an increase in the number of deaths in patients treated with DIPRIVAN as compared to SSAs. Of the 25 patients who died during the trial or within the 28-day follow-up period: 12 (11% were) in the DIPRIVAN 2% treatment group, 9 (8% were) in the DIPRIVAN 1% treatment group, and 4% were (4%) in the SSA treatment group. The differences in mortality rate between the groups were not statistically significant. Review of the deaths failed to reveal a correlation with underlying disease status or a correlation to the drug or a definitive pattern to the causes of death.

Cardiac Anesthesia

DIPRIVAN Injectable Emulsion was evaluated in clinical trials involving patients undergoing coronary artery bypass graft (CABG).

In post-CABG (coronary artery bypass graft) patients, the maintenance rate of propofol administration was usually low (median 11 mcg/kg/min) due to the intraoperative administration of high opioid doses. Patients receiving DIPRIVAN Injectable Emulsion required 35% less nitroprusside than midazolam patients. During initiation of sedation in post-CABG patients, a 15% to 20% decrease in blood pressure was seen in the first 60 minutes. It was not possible to determine cardiovascular effects in patients with severely compromised ventricular function.

INDICATIONS AND USAGE:

DIPRIVAN Injectable Emulsion is an IV sedative-hypnotic agent that can be used as described in the table below.

Table 3. Indications for DIPRIVAN Injectable Emulsion

Indication	**Approved Patient Population**
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see **PRECAUTIONS**)
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

Safety, effectiveness and dosing guidelines for DIPRIVAN Injectable Emulsion have not been established for MAC Sedation in the pediatric population; therefore, it is not recommended for this use (see **PRECAUTIONS, *Pediatric Use***).

DIPRIVAN Injectable Emulsion is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.

In the Intensive Care Unit (ICU), DIPRIVAN Injectable Emulsion can be administered to intubated, mechanically ventilated adult patients to provide continuous sedation and control of stress responses only by persons skilled in the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management.

DIPRIVAN Injectable Emulsion is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established (see **PRECAUTIONS, *Pediatric Use***).

DIPRIVAN Injectable Emulsion is not recommended for obstetrics, including Cesarean section deliveries. DIPRIVAN Injectable Emulsion crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injectable Emulsion may be associated with neonatal depression (see **PRECAUTIONS**).

DIPRIVAN Injectable Emulsion is not recommended for use in nursing mothers because DIPRIVAN Injectable Emulsion has been reported to be excreted in human milk, and the effects of oral absorption of small amounts of propofol are not known (see **PRECAUTIONS**).

CONTRAINDICATIONS:

DIPRIVAN Injectable Emulsion is contraindicated in patients with a known hypersensitivity to DIPRIVAN Injectable Emulsion or any of its components.

DIPRIVAN Injectable Emulsion is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products.

WARNINGS:

Use of DIPRIVAN Injectable Emulsion has been associated with both fatal and life-threatening anaphylactic and anaphylactoid reactions.

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid bolus administration, especially in the elderly, debilitated, or ASA-PS III or IV patients.

For sedation of intubated, mechanically ventilated patients in the Intensive Care Unit (ICU), DIPRIVAN Injectable Emulsion should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.

Use of DIPRIVAN Injectable Emulsion infusions for both adult and pediatric ICU sedation has been associated with a constellation of metabolic derangements and organ system failures, referred to as Propofol Infusion Syndrome, that have resulted in death. The syndrome is characterized by severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, hepatomegaly, cardiac and renal failure. The following appear to be 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 prolonged, high-dose infusions of propofol (> 5 mg/kg/h for > 48h). The syndrome has also been reported following large-dose, short-term infusions during surgical anesthesia. In the setting of prolonged need for sedation, increasing propofol dose requirements to maintain a constant level of sedation, or onset of metabolic acidosis during administration of a propofol infusion, consideration should be given to using alternative means of sedation.

Abrupt discontinuation of DIPRIVAN Injectable Emulsion prior to weaning or for daily evaluation of sedation levels should be avoided. This may result in rapid awakening with associated anxiety, agitation, and resistance to mechanical ventilation. Infusions of DIPRIVAN Injectable Emulsion should be adjusted to maintain a light level of sedation through the weaning process or evaluation of sedation level (see **PRECAUTIONS**).

DIPRIVAN Injectable Emulsion should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. *In vitro* tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance of these findings is not known.

There have been reports in which failure to use aseptic technique when handling Diprivan Injectable Emulsion was associated with microbial contamination of the product and with fever, infection, sepsis, other life-threatening illness, and death. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see DOSAGE AND ADMINISTRATION, *Handling Procedures*).

PRECAUTIONS:

General

Adult and Pediatric Patients

A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated, or ASA-PS III or IV patients (see **DOSAGE AND ADMINISTRATION**). Patients should be continuously monitored for early signs of hypotension and/or bradycardia. Apnea requiring ventilatory support often occurs during induction and may persist for more than 60 seconds. DIPRIVAN Injectable Emulsion use requires caution when administered to patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Very rarely the use of DIPRIVAN Injectable Emulsion 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 brief period of wakefulness. Recovery is spontaneous.

When DIPRIVAN Injectable Emulsion is administered to an epileptic patient, there is a risk of seizure during the recovery phase.

Attention should be paid to minimize pain on administration of DIPRIVAN Injectable Emulsion. Transient local pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Pain during intravenous injection may also be reduced by prior injection of IV lidocaine (1 mL of a 1% solution). Pain on injection occurred frequently in pediatric patients (45%) when a small vein of the hand was utilized without lidocaine pretreatment. With lidocaine pretreatment or when antecubital veins were utilized, pain was minimal (incidence less than 10%) and well-tolerated. There have been reports in the literature indicating that the addition of lidocaine to DIPRIVAN in quantities greater than 20 mg lidocaine/200 mg DIPRIVAN results in instability of the emulsion which is associated with increases in globule sizes over time and (in rat studies) a reduction in anesthetic potency. Therefore, it is recommended that lidocaine be administered prior to DIPRIVAN administration or that it be added to DIPRIVAN immediately before administration and in quantities not exceeding 20 mg lidocaine/200 mg DIPRIVAN.

Venous sequelae, i.e., phlebitis or thrombosis, have been reported rarely (<1%). In two clinical studies using dedicated intravenous catheters, no instances of venous sequelae were observed up to 14 days following induction.

Intra-arterial injection in animals did not induce local tissue effects. Accidental intra-arterial injection has been reported in patients, and, other than pain, there were no major sequelae.

Intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. During the post-marketing period, there have been rare reports of local pain, swelling, blisters, and/or tissue necrosis following accidental extravasation of DIPRIVAN Injectable Emulsion.

Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in association with DIPRIVAN Injectable Emulsion administration.

Clinical features of anaphylaxis, including angioedema, bronchospasm, erythema, and hypotension, occur rarely following DIPRIVAN Injectable Emulsion administration.

There have been rare reports of pulmonary edema in temporal relationship to the administration of DIPRIVAN Injectable Emulsion, although a causal relationship is unknown.

Rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which DIPRIVAN Injectable Emulsion was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to DIPRIVAN Injectable Emulsion is unclear.

DIPRIVAN Injectable Emulsion has no vagolytic activity. Reports of bradycardia, asystole, and rarely, cardiac arrest have been associated with DIPRIVAN Injectable Emulsion. Pediatric patients are susceptible to this effect, particularly when fentanyl is given concomitantly. The intravenous administration of anticholinergic agents (e.g., atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (e.g., succinylcholine) or surgical stimuli.

Intensive Care Unit Sedation

Adult Patients

(See WARNINGS and DOSAGE AND ADMINISTRATION, *Handling Procedures*.) The administration of DIPRIVAN Injectable Emulsion should be initiated as a continuous infusion and changes in the rate of administration made slowly (>5 min) in order to minimize hypotension and avoid acute overdosage (see **DOSAGE AND ADMINISTRATION**).

Patients should be monitored for early signs of significant hypotension and/or cardiovascular depression, which may be profound. These effects are responsive to discontinuation of DIPRIVAN Injectable Emulsion, IV fluid administration, and/or vasopressor therapy. In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus administration should not be used during sedation in order to minimize undesirable cardiorespiratory depression, including hypotension, apnea, airway obstruction, and oxygen desaturation.

As with other sedative medications, there is wide interpatient variability in DIPRIVAN Injectable Emulsion dosage requirements, and these requirements may change with time.

Failure to reduce the infusion rate in patients receiving DIPRIVAN Injectable Emulsion for extended periods may result in excessively high blood concentrations of the drug. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of DIPRIVAN Injectable Emulsion infusion for ICU sedation, especially when it is used for long durations.

Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation. Infusions of DIPRIVAN Injectable Emulsion should be adjusted to maintain a light level of sedation prior to weaning patients from mechanical ventilatory support. Throughout the weaning process, this level of sedation may be maintained in the absence of respiratory depression. Because of the rapid clearance of DIPRIVAN Injectable Emulsion, abrupt discontinuation of a patient's infusion may result in rapid awakening with associated anxiety, agitation, and resistance to mechanical ventilation, making weaning from mechanical ventilation difficult. It is therefore recommended that administration of DIPRIVAN Injectable Emulsion be continued in order to maintain a light level of sedation throughout the weaning process until 10 to15 minutes prior to extubation, at which time the infusion can be discontinued.

Since DIPRIVAN Injectable Emulsion is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when DIPRIVAN Injectable Emulsion is administered for extended periods of time. Patients at risk of hyperlipidemia should be monitored for increases in serum triglycerides or serum turbidity. Administration of DIPRIVAN Injectable Emulsion should be adjusted if fat is being inadequately cleared from the body. A reduction in the quantity of concurrently administered lipids is indicated to compensate for the amount of lipid infused as part of the DIPRIVAN Injectable Emulsion formulation; 1 mL of DIPRIVAN Injectable Emulsion contains approximately 0.1 g of fat (1.1 kcal).

EDTA is a strong chelator of trace metals — including zinc. Although with DIPRIVAN Injectable Emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN Injectable Emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

In clinical trials mean urinary zinc loss was approximately 2.5 to 3 mg/day in adult patients and 1.5 to 2 mg/day in pediatric patients.

In patients who are predisposed to zinc deficiency, such as those with burns, diarrhea, and/or major sepsis, the need for supplemental zinc should be considered during prolonged therapy with DIPRIVAN Injectable Emulsion.

At high doses (2 to 3 grams per day), EDTA has been reported, on rare occasions, to be toxic to the renal tubules. Studies to date in patients with normal or impaired renal function have not shown any alteration in renal function with DIPRIVAN Injectable Emulsion containing 0.005% disodium edetate. In patients at risk for renal impairment, urinalysis and urine sediment should be checked before initiation of sedation and then be monitored on alternate days during sedation.

The long-term administration of DIPRIVAN Injectable Emulsion to patients with renal failure and/or hepatic insufficiency has not been evaluated.

Neurosurgical Anesthesia

When DIPRIVAN Injectable Emulsion is used in patients with increased intracranial pressure or impaired cerebral circulation, significant decreases in mean arterial pressure should be avoided because of the resultant decreases in cerebral perfusion pressure. To avoid significant hypotension and decreases in cerebral perfusion pressure, an infusion or slow bolus of approximately 20 mg every 10 seconds should be utilized instead of rapid, more frequent, and/or larger boluses of DIPRIVAN Injectable Emulsion. Slower induction, titrated to clinical responses, will generally result in reduced induction dosage requirements (1 to 2 mg/kg). When increased ICP is suspected, hyperventilation and hypocarbia should accompany the administration of DIPRIVAN Injectable Emulsion (see **DOSAGE AND ADMINISTRATION**).

Cardiac Anesthesia

Slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shifts, and patients who are hemodynamically unstable. Fluid deficits should be corrected prior to administration of DIPRIVAN Injectable Emulsion. In those patients where additional fluid therapy may be contraindicated, other measures, e.g., elevation of lower extremities, or use of pressor agents, may be useful to offset the hypotension which is associated with the induction of anesthesia with DIPRIVAN Injectable Emulsion.

Information for Patients

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation.

Drug Interactions

The induction dose requirements of DIPRIVAN Injectable Emulsion may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (e.g., morphine, meperidine, and fentanyl, etc.) and combinations of opioids and sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of DIPRIVAN Injectable Emulsion and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia or sedation, the rate of DIPRIVAN Injectable Emulsion administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (e.g., nitrous oxide or opioids). The concurrent administration of potent inhalational agents (e.g., isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injectable Emulsion has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injectable Emulsion.

DIPRIVAN Injectable Emulsion does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g., succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed in adults. In pediatric patients, administration of fentanyl concomitantly with DIPRIVAN Injectable Emulsion may result in serious bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of propofol.

Mutagenesis

Propofol was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. Propofol was not mutagenic in either the gene mutation/gene conversion test using *Saccharomyces cerevisiae*, or *in vitro* cytogenetic studies in Chinese hamsters. In the *in vivo* mouse micronucleus assay with Chinese Hamsters propofol administration did not produce chromosome aberrations.

Impairment of Fertility

Female Wistar rats were administered either 0, 10, or 15 mg/kg/day propofol intravenously from 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m^2 basis) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m^2 basis). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

DIPRIVAN Injectable Emulsion is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN Injectable Emulsion crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injectable Emulsion may be associated with neonatal depression.

Nursing Mothers

DIPRIVAN Injectable Emulsion is not recommended for use in nursing mothers because DIPRIVAN Injectable Emulsion has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use

The safety and effectiveness of DIPRIVAN Injectable Emulsion have been established for induction of anesthesia in pediatric patients aged 3 years and older and for the maintenance of anesthesia aged 2 months and older.

DIPRIVAN Injectable Emulsion is not recommended for the induction of anesthesia in patients younger than 3 years of age and for the maintenance of anesthesia in patients younger than 2 months of age as safety and effectiveness have not been established.

In pediatric patients, administration of fentanyl concomitantly with DIPRIVAN Injectable Emulsion may result in serious bradycardia (see **PRECAUTIONS, *General***).

DIPRIVAN Injectable Emulsion is not indicated for use in pediatric patients for ICU sedation or for MAC sedation for surgical, nonsurgical or diagnostic procedures as safety and effectiveness have not been established.

There have been anecdotal reports of serious adverse events and death in pediatric patients with upper respiratory tract infections receiving DIPRIVAN Injectable Emulsion for ICU sedation.

In one multicenter clinical trial of ICU sedation in critically ill pediatric patients that excluded patients with upper respiratory tract infections, the incidence of mortality observed in patients who received DIPRIVAN Injectable Emulsion (n=222) was 9%, while that for patients who received standard sedative agents (n=105) was 4%. While causality has not been established, DIPRIVAN Injectable Emulsion is not indicated for sedation in pediatric patients until further studies have been performed to document its safety in that population (see **CLINICAL PHARMACOLOGY, *Pharmacokinetics*, Pediatric Patients** and **DOSAGE AND ADMINISTRATION**).

In pediatric patients, abrupt discontinuation following prolonged infusion may result in flushing of the hands and feet, agitation, tremulousness and hyperirritability. Increased incidences of bradycardia (5%), agitation (4%), and jitteriness (9%) have also been observed.

Geriatric Use

The effect of age on induction dose requirements for propofol was assessed in an open-label study involving 211 unpremedicated patients with approximately 30 patients in each decade between the ages of 16 and 80. The average dose to induce anesthesia was calculated for patients up to 54 years of age and for patients 55 years of age or older. The average dose to induce anesthesia in patients up to 54 years of age was 1.99 mg/kg and in patients above 54 it was 1.66 mg/kg. Subsequent clinical studies have demonstrated lower dosing requirements for subjects greater than 60 years of age.

A lower induction dose and a slower maintenance rate of administration of DIPRIVAN Injectable Emulsion should be used in elderly patients. In this group of patients, rapid (single or repeated) bolus administration should not be used in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation. All dosing should be titrated according to patient condition and response (see **DOSAGE AND ADMINISTRATION, Elderly, Debilitated or ASA-PS III or IV Patients** and **CLINICAL PHARMACOLOGY, *Geriatrics*).**

ADVERSE REACTIONS:

General

Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are also derived from publications and marketing experience in over 8 million patients; there are insufficient data to support an accurate estimate of their incidence rates. These studies were conducted using a variety of premedicants, varying lengths of surgical/diagnostic procedures, and various other anesthetic/sedative agents. Most adverse events were mild and transient.

Anesthesia and MAC Sedation in Adults

The following estimates of adverse events for DIPRIVAN Injectable Emulsion include data from clinical trials in general anesthesia/MAC sedation (N=2889 adult patients). The adverse events listed below as probably causally related are those events in which the actual incidence rate in patients treated with DIPRIVAN Injectable Emulsion was greater than the comparator incidence rate in these trials. Therefore, incidence rates for anesthesia and MAC sedation in adults generally represent estimates of the percentage of clinical trial patients which appeared to have probable causal relationship.

The adverse experience profile from reports of 150 patients in the MAC sedation clinical trials is similar to the profile established with DIPRIVAN Injectable Emulsion during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea.

Anesthesia in Pediatric Patients

Generally the adverse experience profile from reports of 506 DIPRIVAN Injectable Emulsion pediatric patients from 6 days through 16 years of age in the US/Canadian anesthesia clinical trials is similar to the profile established with DIPRIVAN Injectable Emulsion during anesthesia in adults (see Pediatric percentages [Peds %] below). Although not reported as an adverse event in clinical trials, apnea is frequently observed in pediatric patients.

ICU Sedation in Adults

The following estimates of adverse events include data from clinical trials in ICU sedation (N=159 adult patients). Probably related incidence rates for ICU sedation were determined by individual case report form review. Probable causality was based upon an apparent dose response relationship and/or positive responses to rechallenge. In many instances the presence of concomitant disease and concomitant therapy made the causal relationship unknown. Therefore, incidence rates for ICU sedation generally represent estimates of the percentage of clinical trial patients which appeared to have a probable causal relationship.

Incidence greater than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	**ICU Sedation**
Cardiovascular:	Bradycardia	Bradycardia
	Arrhythmia [Peds: 1.2%]	
	Tachycardia Nodal [Peds: 1.6%]	
	Hypotension* [Peds: 17%] (see also **CLINICAL PHARMACOLOGY**)	Decreased Cardiac Output
	Hypertension [Peds: 8%]	Hypotension 26%
Central Nervous System:	Movement* [Peds: 17%]	
Injection Site:	Burning/Stinging or Pain, 17.6% [Peds: 10%]	
Metabolic/Nutritional:		Hyperlipemia*
Respiratory:	Apnea (see also **CLINICAL PHARMACOLOGY**)	Respiratory Acidosis During Weaning*
Skin and Appendages:	Rash [Peds: 5%] Pruritus [Peds: 2%]	

Events without an * or % had an incidence of 1% to 3%
*Incidence of events 3% to 10%

Incidence less than 1% - Probably Causally Related

	Anesthesia/MAC Sedation	**ICU Sedation**
Body as a Whole:	Anaphylaxis/Anaphylactoid Reaction Perinatal Disorder [Tachycardia] [Bigeminy] [Bradycardia] [Premature Ventricular Contractions] [Hemorrhage] [ECG Abnormal] [Arrhythmia Atrial] [Fever] [Extremities Pain] [Anticholinergic Syndrome]	
Cardiovascular:	Premature Atrial Contractions Syncope	
Central Nervous System:	Hypertonia/Dystonia, Paresthesia	Agitation
Digestive:	[Hypersalivation] [Nausea]	
Hemic/Lymphatic:	[Leukocytosis]	
Injection Site:	[Phlebitis] [Pruritus]	
Metabolic:	[Hypomagnesemia]	
Musculoskeletal:	Myalgia	
Nervous:	[Dizziness] [Agitation] [Chills] [Somnolence] [Delirium]	
Respiratory:	Wheezing [Cough] [Laryngospasm] [Hypoxia]	Decreased Lung Function
Skin and Appendages:	Flushing, Pruritus	
Special Senses:	Amblyopia [Vision Abnormal]	
Urogenital:	Cloudy Urine	Green Urine

Incidence less than 1% - Causal Relationship Unknown

	Anesthesia/MAC Sedation	**ICU Sedation**
Body as a Whole:	Asthenia, Awareness, Chest Pain, Extremities Pain, Fever, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain	Fever, Sepsis, Trunk Pain, Whole Body Weakness
Cardiovascular:	Arrhythmia, Atrial Fibrillation, Atrioventricular Heart Block, Bigeminy, Bleeding, Bundle Branch Block, Cardiac Arrest, ECG Abnormal, Edema, Extrasystole, Heart Block, Hypertension, Myocardial Infarction, Myocardial Ischemia, Premature Ventricular Contractions, ST Segment Depression, Supraventricular Tachycardia, Tachycardia, Ventricular Fibrillation	Arrhythmia, Atrial Fibrillation, Bigeminy, Cardiac Arrest, Extrasystole, Right Heart Failure, Ventricular Tachycardia
Central Nervous System:	Abnormal Dreams, Agitation, Amorous Behavior, Anxiety, Bucking/Jerking/Thrashing, Chills/Shivering/Clonic/Myoclonic Movement, Combativeness, Confusion, Delirium, Depression, Dizziness, Emotional Lability, Euphoria, Fatigue, Hallucinations, Headache, Hypotonia, Hysteria, Insomnia, Moaning, Neuropathy, Opisthotonos, Rigidity, Seizures, Somnolence, Tremor, Twitching	Chills/Shivering, Intracranial Hypertension, Seizures, Somnolence, Thinking Abnormal
Digestive:	Cramping, Diarrhea, Dry Mouth, Enlarged Parotid, Nausea, Swallowing, Vomiting	Ileus, Liver Function Abnormal
Hematologic/Lymphatic:	Coagulation Disorder, Leukocytosis	
Injection Site:	Hives/Itching, Phlebitis, Redness/Discoloration	
Metabolic/Nutritional:	Hyperkalemia, Hyperlipemia	BUN Increased, Creatinine Increased, Dehydration, Hyperglycemia, Metabolic Acidosis, Osmolality Increased
Respiratory:	Bronchospasm, Burning in Throat, Cough, Dyspnea, Hiccough, Hyperventilation, Hypoventilation, Hypoxia, Laryngospasm, Pharyngitis, Sneezing, Tachypnea, Upper Airway Obstruction	Hypoxia
Skin and Appendages:	Conjunctival Hyperemia, Diaphoresis, Urticaria	Rash
Special Senses:	Diplopia, Ear Pain, Eye Pain, Nystagmus, Taste Perversion, Tinnitus	
Urogenital:	Oliguria, Urine Retention	Kidney Failure

DRUG ABUSE AND DEPENDENCE:

Rare cases of self-administration of DIPRIVAN Injectable Emulsion by health care professionals have been reported, including some fatalities. DIPRIVAN Injectable Emulsion should be managed to prevent the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

OVERDOSAGE:

If overdosage occurs, DIPRIVAN Injectable Emulsion administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents.

DOSAGE AND ADMINISTRATION:

Propofol blood concentrations at steady-state are generally proportional to infusion rates, especially in individual patients. Undesirable effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increases in the infusion rate. An adequate interval (3 to 5 minutes) must be allowed between dose adjustments to allow for and assess the clinical effects.

Shake well before use. Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

When administering DIPRIVAN Injectable Emulsion by infusion, syringe or volumetric pumps are recommended to provide controlled infusion rates. When infusing DIPRIVAN Injectable Emulsion to patients undergoing magnetic resonance imaging, metered control devices may be utilized if mechanical pumps are impractical.

Changes in vital signs indicating a stress response to surgical stimulation or the emergence from anesthesia may be controlled by the administration of 25 mg (2.5 mL) to 50 mg (5 mL) incremental boluses and/or by increasing the infusion rate of DIPRIVAN Injectable Emulsion.

For minor surgical procedures (e.g., body surface) nitrous oxide (60% to 70%) can be combined with a variable rate DIPRIVAN Injectable Emulsion infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (e.g., intra-abdominal), or if supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN Injectable Emulsion and/or opioids should be increased in order to provide adequate anesthesia.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injectable Emulsion at rates higher than are clinically necessary. Generally, rates of 50 to 100 mcg/kg/min in adults should be achieved during maintenance in order to optimize recovery times.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics, and opioids) can increase CNS depression induced by propofol. Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the necessary propofol injection maintenance infusion rate and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication.

Induction of General Anesthesia

Adult Patients

Most adult patients under 55 years of age and classified as ASA-PS I or II require 2 to 2.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injectable Emulsion should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injectable Emulsion.

Elderly, Debilitated, or ASA-PS III or IV Patients

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injectable Emulsion before treating elderly, debilitated, or ASA-PS III or IV patients. Due to the reduced clearance and higher blood concentrations, most of these patients require approximately 1 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN Injectable Emulsion for induction of anesthesia according to their condition and responses. A rapid bolus should not be used, as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation (see **DOSAGE AND ADMINISTRATION**).

Pediatric Patients

Most patients aged 3 years through 16 years and classified ASA-PS I or II require 2.5 to 3.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger pediatric patients may require higher induction doses than older pediatric patients. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injectable Emulsion. A lower dosage is recommended for pediatric patients classified as ASA-PS III or IV. Attention should be paid to minimize pain on injection when administering DIPRIVAN Injectable Emulsion to pediatric patients. Boluses of DIPRIVAN Injectable Emulsion may be administered via small veins if pretreated with lidocaine or via antecubital or larger veins (see **PRECAUTIONS, *General***).

Neurosurgical Patients

Slower induction is recommended using boluses of 20 mg every 10 seconds. Slower boluses or infusions of DIPRIVAN Injectable Emulsion for induction of anesthesia, titrated to clinical responses, will generally result in reduced induction dosage requirements (1 to 2 mg/kg) (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Cardiac Anesthesia

DIPRIVAN Injectable Emulsion has been well-studied in patients with coronary artery disease, but experience in patients with hemodynamically significant valvular or congenital heart disease is limited. As with other anesthetic and sedative-hypnotic agents, DIPRIVAN Injectable Emulsion in healthy patients causes a decrease in blood pressure that is secondary to decreases in preload (ventricular filling volume at the end of the diastole) and afterload (arterial resistance at the beginning of the systole). The magnitude of these changes is proportional to the blood and effect site concentrations achieved. These concentrations depend upon the dose and speed of the induction and maintenance infusion rates.

In addition, lower heart rates are observed during maintenance with DIPRIVAN Injectable Emulsion, possibly due to reduction of the sympathetic activity and/or resetting of the baroreceptor reflexes. Therefore, anticholinergic agents should be administered when increases in vagal tone are anticipated.

As with other anesthetic agents, DIPRIVAN Injectable Emulsion reduces myocardial oxygen consumption. Further studies are needed to confirm and delineate the extent of these effects on the myocardium and the coronary vascular system.

Morphine premedication (0.15 mg/kg) with nitrous oxide 67% in oxygen has been shown to decrease the necessary DIPRIVAN Injectable Emulsion maintenance infusion rates and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication. The rate of DIPRIVAN Injectable Emulsion administration should be determined based on the patient's premedication and adjusted according to clinical responses.

A rapid bolus induction should be avoided. A slow rate of approximately 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg) should be used. In order to assure adequate anesthesia, when DIPRIVAN Injectable Emulsion is used as the primary agent, maintenance infusion rates should not be less than 100 mcg/kg/min and should be supplemented with analgesic levels of continuous opioid administration. When an opioid is used as the primary agent, DIPRIVAN Injectable Emulsion maintenance rates should not be less than 50 mcg/kg/min, and care should be taken to ensure amnesia. Higher doses of DIPRIVAN Injectable Emulsion will reduce the opioid requirements (see Table 4). When DIPRIVAN Injectable Emulsion is used as the primary anesthetic, it should not be administered with the high-dose opioid technique as this may increase the likelihood of hypotension (see **PRECAUTIONS, Cardiac Anesthesia**).

Table 4. Cardiac Anesthesia Techniques

Primary Agent	Rate	Secondary Agent/Rate (Following Induction with Primary Agent)
DIPRIVAN Injectable Emulsion		OPIOID[a]/0.05 to 0.075 mcg/kg/min (no bolus)
Preinduction Anxiolysis	25 mcg/kg/min	
Induction	0.5 to 1.5 mg/kg over 60 sec	
Maintenance (Titrated to Clinical Response)	100 to150 mcg/kg/min	
OPIOID[b]		DIPRIVAN Injectable Emulsion/50 to 100 mcg/kg/min (no bolus)
Induction	25 to 50 mcg/kg	
Maintenance	0.2 to 0.3 mcg/kg/min	

[a]OPIOID is defined in terms of fentanyl equivalents, i.e.,
1 mcg of fentanyl = 5 mcg of alfentanil (for bolus)
= 10 mcg of alfentanil (for maintenance)
or
= 0.1 mcg of sufentanil

[b]Care should be taken to ensure amnesia.

Maintenance of General Anesthesia

Adult Patients

In adults, anesthesia can be maintained by administering DIPRIVAN Injectable Emulsion by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

Continuous Infusion

DIPRIVAN Injectable Emulsion 100 to 200 mcg/kg/min administered in a variable rate infusion with 60% to 70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injectable Emulsion should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction dose, higher rates of infusion are generally required (150 to 200 mcg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased 30% to 50% during the first half-hour of maintenance. Generally, rates of 50 to 100 mcg/kg/min in adults should be achieved during maintenance in order to optimize recovery times.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics, and opioids) can increase the CNS depression induced by propofol.

Intermittent Bolus

Increments of DIPRIVAN Injectable Emulsion 25 mg (2.5 mL) to 50 mg (5 mL) may be administered with nitrous oxide in adult patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

Pediatric Patients

DIPRIVAN Injectable Emulsion administered as a variable rate infusion supplemented with nitrous oxide 60% to 70% provides satisfactory anesthesia for most children 2 months of age or older, ASA-PS I or II, undergoing general anesthesia.

In general, for the pediatric population, maintenance by infusion of DIPRIVAN Injectable Emulsion at a rate of 200 to 300 mcg/kg/min should immediately follow the induction dose. Following the first half-hour of maintenance, infusion rates of 125 to 150 mcg/kg/min are typically needed. DIPRIVAN Injectable Emulsion should be titrated to achieve the desired clinical effect. Younger pediatric patients may require higher maintenance infusion rates than older pediatric patients. (See Table 2 Clinical Trials.)

DIPRIVAN Injectable Emulsion has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and opioid analgesics, as well as with inhalational and regional anesthetic agents.

In the elderly, debilitated, or ASA-PS III or IV patients, rapid bolus doses should not be used, as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction, and oxygen desaturation.

Monitored Anesthesia Care (MAC) Sedation

Adult Patients

When DIPRIVAN Injectable Emulsion is administered for MAC sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of DIPRIVAN Injectable Emulsion administration will be in the range of 25 to 75 mcg/kg/min.

During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus dose administration. In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). A rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and oxygen desaturation.

DIPRIVAN® (propofol) Injectable Emulsion, USP

Initiation of MAC Sedation

For initiation of MAC sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injectable Emulsion at 100 to 150 mcg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the desired clinical effect while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injectable Emulsion is administered slowly over 3 to 5 minutes, most patients will be adequately sedated, and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels.

In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). The rate of administration should be over 3 to 5 minutes and the dosage of DIPRIVAN Injectable Emulsion should be reduced to approximately 80% of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs (see **DOSAGE AND ADMINISTRATION**).

Maintenance of MAC Sedation

For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 mcg/kg/min (1.5 to 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance. Infusion rates should subsequently be decreased over time to 25 to 50 mcg/kg/min and adjusted to clinical responses. In titrating to clinical effect, allow approximately 2 minutes for onset of peak drug effect.

Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of DIPRIVAN Injectable Emulsion at rates higher than are clinically necessary.

If the intermittent bolus dose method is used, increments of DIPRIVAN Injectable Emulsion 10 mg (1 mL) or 20 mg (2 mL) can be administered and titrated to desired clinical effect. With the intermittent bolus method of sedation maintenance, there is increased potential for respiratory depression, transient increases in sedation depth, and prolongation of recovery.

In the elderly, debilitated, or ASA-PS III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation (see **WARNINGS**). The rate of administration and the dosage of DIPRIVAN Injectable Emulsion should be reduced to approximately 80% of the usual adult dosage in these patients according to their condition, responses, and changes in vital signs (see **DOSAGE AND ADMINISTRATION**).

DIPRIVAN Injectable Emulsion can be administered as the sole agent for maintenance of MAC sedation during surgical/diagnostic procedures. When DIPRIVAN Injectable Emulsion sedation is supplemented with opioid and/or benzodiazepine medications, these agents increase the sedative and respiratory effects of DIPRIVAN Injectable Emulsion and may also result in a slower recovery profile (see **PRECAUTIONS, *Drug Interactions***).

ICU Sedation

(See WARNINGS and DOSAGE AND ADMINISTRATION, *Handling Procedures*.)

Abrupt discontinuation of DIPRIVAN Injectable Emulsion prior to weaning or for daily evaluation of sedation levels should be avoided. This may result in rapid awakening with associated anxiety, agitation, and resistance to mechanical ventilation. Infusions of DIPRIVAN Injectable Emulsion should be adjusted to assure a minimal level of sedation is maintained throughout the weaning process and when assessing the level of sedation (see **PRECAUTIONS**).

Adult Patients

For intubated, mechanically ventilated adult patients, Intensive Care Unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension (see **DOSAGE AND ADMINISTRATION**).

Most adult ICU patients recovering from the effects of general anesthesia or deep sedation will require maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) individualized and titrated to clinical response (see **DOSAGE AND ADMINISTRATION**). With medical ICU patients or patients who have recovered from the effects of general anesthesia or deep sedation, the rate of administration of 50 mcg/kg/min or higher may be required to achieve adequate sedation. These higher rates of administration may increase the likelihood of patients developing hypotension. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**).

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors including the patient's underlying medical problems, preinduction and concomitant medications, age, ASA-PS classification, and level of debilitation of the patient. The elderly, debilitated, and ASA-PS III or IV patients may have exaggerated hemodynamic and respiratory responses to rapid bolus doses (see **WARNINGS**).

DIPRIVAN Injectable Emulsion should be individualized according to the patient's condition and response, blood lipid profile, and vital signs (see **PRECAUTIONS, *Intensive Care Unit Sedation***). For intubated, mechanically ventilated adult patients, Intensive Care Unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. When indicated, initiation of sedation should begin at 5 mcg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Most adult patients require maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**). Dosages of DIPRIVAN Injectable Emulsion should be reduced in patients who have received large dosages of narcotics. Conversely, the DIPRIVAN Injectable Emulsion dosage requirement may be reduced by adequate management of pain with analgesic agents. As with other sedative medications, there is interpatient variability in dosage requirements, and these requirements may change with time (see **SUMMARY OF DOSAGE GUIDELINES**). Evaluation of level of sedation and assessment of cns function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN required for sedation (see ***Clinical Trials*, Intensive Care Unit (ICU) Sedation**). Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur. Patients with compromised myocardial function, intravascular volume depletion, or abnormally low vascular tone (e.g., sepsis) may be more susceptible to hypotension (see **PRECAUTIONS**).

SUMMARY OF DOSAGE GUIDELINES:

Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosing requirements for induction of anesthesia in pediatric patients have only been established for children 3 years of age or older. Safety and dosing requirements for the maintenance of anesthesia have only been established for children 2 months of age and older.

For complete dosage information, see **DOSAGE AND ADMINISTRATION**.

INDICATION	DOSAGE AND ADMINISTRATION
Induction of General Anesthesia:	**Healthy Adults Less Than 55 Years of Age:** 40 mg every 10 seconds until induction onset (2 to 2.5 mg/kg). **Elderly, Debilitated, or ASA-PS III or IV Patients:** 20 mg every 10 seconds until induction onset (1 to 1.5 mg/kg). **Cardiac Anesthesia:** 20 mg every 10 seconds until induction onset (0.5 to 1.5 mg/kg). **Neurosurgical Patients:** 20 mg every 10 seconds until induction onset (1 to 2 mg/kg) **Pediatric Patients - healthy, from 3 years to 16 years of age:** 2.5 to 3.5 mg/kg administered over 20 to 30 seconds. (see **PRECAUTIONS, *Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Infusion** **Healthy Adults Less Than 55 Years of Age:** 100 to 200 mcg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, ASA-PS III or IV Patients:** 50 to 100 mcg/kg/min (3 to 6 mg/kg/h). **Cardiac Anesthesia:** Most patients require: Primary DIPRIVAN Injectable Emulsion with Secondary Opioid – 100 to 150 mcg/kg/min Low-Dose DIPRIVAN Injectable Emulsion with Primary Opioid – 50 to 100 mcg/kg/min (see **DOSAGE AND ADMINISTRATION**, Table 4) **Neurosurgical Patients:** 100 to 200 mcg/kg/min (6 to 12 mg/kg/h). **Pediatric Patients - healthy, from 2 months of age to 16 years of age:** 125 to 300 mcg/kg/min (7.5 to 18 mg/kg/h) Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased. (see **PRECAUTIONS, *Pediatric Use*** and **CLINICAL PHARMACOLOGY, Pediatrics**)
Maintenance of General Anesthesia:	**Intermittent Bolus** **Healthy Adults Less Than 55 Years of Age:** Increments of 20 to 50 mg as needed.
Initiation of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100 to 150 mcg/kg/min (6 to 9 mg/kg/h) for 3 to 5 minutes or a slow injection of 0.5 mg/kg over 3 to 5 minutes followed immediately by a maintenance infusion. **Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (see **WARNINGS**).
Maintenance of MAC Sedation:	**Healthy Adults Less Than 55 Years of Age:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 mcg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **In Elderly, Debilitated, Neurosurgical, or ASA-PS III or IV Patients:** Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used (see **WARNINGS**).
Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated	**Adult Patients -** Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 mcg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5 to 10 mcg/kg/min (0.3 to 0.6 mg/kg/h) over 5 to 10 minutes may be used until desired clinical effect is achieved. Maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher may be required. Administration should not exceed 4 mg/kg/hour unless the benefits outweigh the risks (see **WARNINGS**). **Evaluation of clinical effect and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of DIPRIVAN Injectable Emulsion required for sedation.** **The tubing and any unused portions of DIPRIVAN Injectable Emulsion should be discarded after 12 hours because DIPRIVAN Injectable Emulsion contains no preservatives and is capable of supporting growth of microorganisms (see WARNINGS and DOSAGE AND ADMINISTRATION).**

Administration with Lidocaine

If lidocaine is to be administered to minimize pain on injection of DIPRIVAN, it is recommended that it be administered prior to DIPRIVAN administration or that it be added to DIPRIVAN immediately before administration and in quantities not exceeding 20 mg lidocaine/200 mg DIPRIVAN.

Compatibility and Stability

DIPRIVAN Injectable Emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration

DIPRIVAN Injectable Emulsion is provided as a ready-to-use formulation. However, should dilution be necessary, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

Administration with Other Fluids

Compatibility of DIPRIVAN Injectable Emulsion with the coadministration of blood/serum/plasma has not been established (see **WARNINGS**). When administered using a y-type infusion set, DIPRIVAN Injectable Emulsion has been shown to be compatible with the following intravenous fluids.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Clinical experience with the use of in-line filters and DIPRIVAN Injectable Emulsion during anesthesia or ICU/MAC sedation is limited. DIPRIVAN Injectable Emulsion should only be administered through a filter with a pore size of 5 micron or greater unless it has been demonstrated that the filter does not restrict the flow of DIPRIVAN Injectable Emulsion and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically appropriate. Continuous monitoring is necessary due to the potential for restricted flow and/or breakdown of the emulsion.

Do not use if there is evidence of separation of the phases of the emulsion.

Rare cases of self-administration of DIPRIVAN Injectable Emulsion by health care professionals have been reported, including some fatalities (see **DRUG ABUSE AND DEPENDENCE**).

Strict aseptic technique must always be maintained during handling. Diprivan Injectable Emulsion is a single-use parenteral product which contains 0.005% disodium edetate to inhibit the rate of growth of microorganisms, up to 12 hours, in the event of accidental extrinsic contamination. However, Diprivan Injectable Emulsion can still support the growth of microorganisms as it is not an antimicrobially preserved product under USP standards. Accordingly, strict aseptic technique must still be adhered to. Do not use if contamination is suspected. Discard unused portions as directed within the required time limits (see DOSAGE AND ADMINISTRATION, *Handling Procedures*). There have been reports in which failure to use aseptic technique when handling Diprivan Injectable Emulsion was associated with microbial contamination of the product and with fever, infection/sepsis, other life-threatening illness, and/or death.

Diprivan, with EDTA inhibits microbial growth for up to 12 hours, as demonstrated by test data for representative USP microorganisms.

Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

DIPRIVAN Injectable Emulsion should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The vial syringe rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injectable Emulsion should be drawn into sterile syringes immediately after vials are opened. When withdrawing DIPRIVAN Injectable Emulsion from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the vial was opened. Administration should commence promptly and be completed within 12 hours after the vials have been opened.

DIPRIVAN Injectable Emulsion should be prepared for single-patient use only. Any unused portions of DIPRIVAN Injectable Emulsion, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injectable Emulsion must be discarded at the end of the anesthetic procedure or at 12 hours, whichever occurs sooner. The IV line should be flushed every 12 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injectable Emulsion.

Guidelines for Aseptic Technique for ICU Sedation

DIPRIVAN Injectable Emulsion should be prepared for single-patient use only. When DIPRIVAN Injectable Emulsion is administered directly from the vial, strict aseptic techniques must be followed. The vial rubber stopper should be disinfected using 70% isopropyl alcohol. A sterile vent spike and sterile tubing must be used for administration of DIPRIVAN Injectable Emulsion. As with other lipid emulsions, the number of IV line manipulations should be minimized. Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portions of DIPRIVAN Injectable Emulsion must be discarded after 12 hours.

If DIPRIVAN Injectable Emulsion is transferred to a syringe or other container prior to administration, the handling procedures for General anesthesia/MAC sedation should be followed, and the product should be discarded and administration lines changed after 12 hours.

HOW SUPPLIED:

DIPRIVAN Injectable Emulsion, USP is available as follows:

Product No.	NDC No.	Strength	
260920	63323-269-20	1% (10 mg/mL propofol)	20 mL ready-to–use single-patient infusion vial.
260950	63323-269-50	1% (10 mg/mL propofol)	50 mL ready-to–use single-patient infusion vial.
260965	63323-269-65	1% (10 mg/mL propofol)	100 mL ready-to–use single-patient infusion vial.

Propofol undergoes oxidative degradation, in the presence of oxygen, and is therefore packaged under nitrogen to eliminate this degradation path.

Store between 4° to 22°C (40° to 72°F). Do not freeze. Shake well before use.

Manufactured for:

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

Made in Italy

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