CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-627 / S-002

Trade Name: **Diprivan**

Generic Name: **propofol**

Sponsor: **ICI Pharmaceuticals**

Approval Date: **December 31, 1991**

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APPLICATION NUMBER:

19-627 / S-002

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 19-627/S-002

DEC 31 1991

ICI Pharmaceuticals Group
Wilmington, Delaware 19897

ATTENTION: Nanette E. Nolston
Assistant Manager, Drug Registration
Drug Regulatory Affairs Department

Dear Ms. Nolston:

Reference is made to your supplemental new drug application dated March 30 1990, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the product DIPRIVAN (propofol). Reference is also made to your amendments dated July 11, November 26, December 20, 27, and 31, 1991.

The supplemental application provides revised labeling with changes to the Clinical Pharmacology, Indications and Usage, Contraindicatons, Precautions, Adverse Reactions, and Dosage and Administration sections and was submitted under 21 CFR 314.70 (c)(2)a(1) "Changes Being Effected".

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommeded in the draft labeling dated December 31, 1991 . Accordingly, the application, with these labeling revisions, is approved effective as of the date of this letter. Should you have any questions, please contact the undersigned at (301) 443-3761.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 19-627". Approval of the submission by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available further revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Sharon A. Schmidt
Project Manager
Pilot Drug Evaluation Staff, HFD-007
Center for Drug Evaluation & Research

cc:
Orig. NDA 19-627/S-002/
HFD-007/Division File
HFD-007/D.Scally
HFD-007/S.Schmidt/12/27/91
HFD-80
HFD-730
HFD-232
HFC-130/Jallen
R/D Init. by: S.Barnes, 12/31/91
F/T by: by RTuanmu, 12/31/91
Wang #2216P
SUPPLEMENTAL NDA LABELING APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-002

LABELING

~~REV D 02/01 SIC 64022-04~~

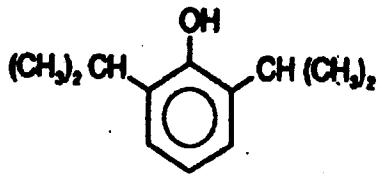
Revise to: REV H 06/91, SIC XXXXX-XX

PROFESSIONAL INFORMATION BROCHURE

DIPRIVAN ® (propofol) Injection EMULSION FOR IV ADMINISTRATION

DESCRIPTION

DIPRIVAN® (propofol) Injection is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-Diisopropylphenol and has a molecular weight of 178.27. The empirical and structural formulas are:



$C_{12}H_{18}O$

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The emulsion is isotonic and has a pH of 7.0 - 8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL); with sodium hydroxide to adjust pH.

DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

CLINICAL PHARMACOLOGY

DIPRIVAN Injection is an intravenous hypnotic agent for use in the induction and maintenance ~~of anesthesia~~. The pharmacokinetic profile of DIPRIVAN Injection can be characterized as follows: After a single rapid IV bolus dose, two distribution phases are seen, a rapid phase with a half-life of 1.8 to 8.3 min and a slower phase of 34 to 64 min. These distribution phases are associated with the movement of DIPRIVAN from highly perfused tissues (vessel-rich tissues) to less, well-perfused tissues. The terminal elimination half-life of DIPRIVAN ranges from 300 to 700 min. With prolonged administration of DIPRIVAN Injection, the terminal elimination half-life may become extended beyond 700 min. DIPRIVAN has a high metabolic

Revise to: " ... of anesthesia or sedation."

clearance that ranges from 1.6 L/min to 3.4 L/min in healthy 70 kg patients. This metabolic clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism. DIPRIVAN has a large steady state distribution volume that ranges from 150 to 1,000 liters in healthy 70 kg patients. The long terminal elimination half-life of DIPRIVAN is due to the large steady state distribution volume which is presumed to be due to extensive drug partitioning into tissues.

The termination of anesthetic drug effects of DIPRIVAN after a single IV bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance both of which will decrease blood concentrations. Recovery from anesthesia is rapid. Following induction (2.0 to 2.5 mg/kg DIPRIVAN Injection) and maintenance (~~0.1 to 0.2 mg/kg/min~~) of anesthesia for periods up to two hours, the majority of patients are generally awake, responsive to verbal commands, and oriented within 8 minutes. Recovery from the effects of DIPRIVAN Injection occurs due to metabolism and distribution during the first two exponents of the decay curve and is not dependent on the terminal elimination half-life. A study in six subjects showed approximately 70% of the administered radiolabeled DIPRIVAN Injection dose was recovered in the urine in the first 24 hours and approximately 90% of the dose was recovered in the urine within five days. DIPRIVAN is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. A glucuronide conjugation metabolite accounted for about 50% of the administered dose. The exact metabolic fate of DIPRIVAN and the sites of possible "extrahepatic" metabolism have not been identified.

Revise to: "(100 to 200 µg/kg/min)"

The pharmacokinetics of DIPRIVAN Injection do not appear to be altered by gender, chronic hepatic cirrhosis or chronic renal failure. The effects of acute hepatic or renal failure on the pharmacokinetics of DIPRIVAN have not been studied. With increasing age the clearance of DIPRIVAN decreases from a mean ± S.D. of 1.8 ± 0.4 L/min in young (18-35 years) patients to a value of 1.4 ± 0.4 L/min in elderly (65-80 years) patients. When given by an infusion for up to two hours, the pharmacokinetics of DIPRIVAN appear to be independent of dose (~~0.05 – 0.15 mg/kg/min~~) and similar to IV bolus pharmacokinetics. The steady state propofol blood concentrations are proportional to the rate of administration.

Revise to: "(50 to 150 µg/kg/min)"

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics and narcotics)

can increase the CNS depression induced by DIPRIVAN. Morphine premedication (0.15 mg/kg) with N_2O 67% has been shown to decrease the necessary DIPRIVAN Injection maintenance infusion rate and therapeutic blood concentrations, when compared to a nonnarcotic (lorazepam) premedication. An alfentanil infusion rate of 50 ug/kg/h has been shown to replace the anesthetic effects of N_2O 67% and morphine premedication.

Intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly with minimal excitation, usually within 40 seconds from the start of an injection (one arm-brain circulation time). As with other rapidly acting intravenous anesthetic agents, the half-time of blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Propofol blood concentrations required for maintenance ~~of anesthesia~~ have not been completely characterized.

Revise to: "...of anesthesia or sedation ..."

When nitrous oxide, oxygen, and propofol are used for maintenance of general anesthesia, supplementation with analgesic agents (eg, narcotics) is generally required; neuromuscular blocking agents may also be required. (See DOSAGE AND ADMINISTRATION).

The hemodynamic effects of DIPRIVAN Injection during induction ~~of anesthesia vary~~. If spontaneous ventilation is maintained, the major cardiovascular effects are 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), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (eg, fentanyl) when used as a premedicant further decreases cardiac output.

Revise to: "... of anesthesia or sedation vary."

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

Revise to: "... anesthesia or sedation ..."

Insufficient data are available regarding the cardiovascular effects of DIPRIVAN Injection when used for induction and/or maintenance ~~of anesthesia~~ in elderly, hypovolemic, hypotensive, debilitated patients, patients with severe cardiac disease (ejection fraction <50%) or other

Revise to: "... of anesthesia or sedation ..."

ASA III/IV patients. However, limited information suggests that these patients may have more profound adverse cardiovascular responses. It is recommended that if DIPRIVAN Injection is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug be used. (See DOSAGE AND ADMINISTRATION.)

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

Induction of anesthesia with DIPRIVAN Injection is frequently associated with apnea. In 1573 patients who received DIPRIVAN Injection (2.0 to 2.5 mg/kg), apnea lasted 0-30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. During maintenance DIPRIVAN Injection (~~0.1 to 0.2 mg/kg/min~~) causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (eg, narcotics, sedatives, etc.).

Revise to: "(100 to 200 µg/kg/min)"

Clinical studies in humans and studies in animals show that DIPRIVAN Injection does not suppress the adrenal response to ACTH.

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

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

INDICATIONS AND USAGE

DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

ADD paragraph: "DIPRIVAN Injection, when administered IV as directed, is effective to initiate and maintain sedation for monitored anesthesia care (MAC) during diagnostic procedures. DIPRIVAN Injection may also be used in conjunction with local/regional anesthesia to provide sedation for monitored anesthesia care in patients undergoing surgical procedures. (See PRECAUTIONS.)"

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection 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.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS

When general ~~anesthesia~~ is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

Revise to: "... anesthesia or sedation ..."

WARNINGS

~~DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.~~

Revise to: "For general anesthesia or sedation for monitored anesthesia care, DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. **Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available."**

DIPRIVAN Injection 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 is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in

DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS

General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Add paragraph: "When DIPRIVAN Injection is administered as a sedative for monitored anesthesia care during surgical or diagnostic procedures, oxygen supplementation should be provided where clinically indicated; and oxygen saturation should be monitored on all patients."

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (<1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

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

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

Revise to: "... anesthetic or sedative effects..."

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

Revise to: "... of anesthesia or sedation ..."

Revise to: "... of anesthesia or sedation ..."

Revise to: "... anesthetic or sedative ..."

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

No significant adverse interactions with commonly used premedications or drugs used during ~~anesthesia~~ (including a

Revise to: "... anesthesia or sedation ..."

range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 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 Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) 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 (or 6 times the recommended human induction dose). 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 Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN 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: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS

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 derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% - All events regardless of causality, derived from clinical trials

Body as a Whole: Fever

Cardiovascular: Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension

Central Nervous System: Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement

Digestive: Nausea**, Vomiting*, Abdominal Cramping

Injection Site: Burning/Stinging**, Pain**, Tingling/Numbness, Coldness

Respiratory: Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY)
Skin and Appendages: Flushing

Incidence of unmarked events is 1%-3%.
* 3% to 10%
** 10% or greater

Incidence Less than 1% - Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)
Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain
Cardiovascular: Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression
Central Nervous System: Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity
Digestive: Hypersalivation, Dry Mouth, Swallowing
Injection Site: Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration
Musculoskeletal: Myalgia
Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia
Skin and Appendages: Rash, Urticaria
Special Senses: Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus
Urogenital: Urine Retention, *Green Urine*

Incidence Less than 1% - Causal Relationship Unknown
(Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)
Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, *Myocardial ischemia*
Central Nervous System: Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus*
Digestive: Diarrhea
Respiratory: Laryngospasm
Skin and Appendages: Diaphoresis, Pruritus, *Conjunctival Hyperemia*
Special Senses: Ear Pain, *Nystagmus*
Urogenital: Abnormal Urine

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection 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.

The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION

~~**Induction**~~: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

Delete indentation and revise heading to: **"Induction of Anesthesia"**

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

~~**Maintenance**~~: Anesthesia can be maintained by administering DIPRIVAN Injection 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.

Delete indentation and revise heading to: **Maintenance of Anesthesia"**

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or

volumetric pumps be used to provide controlled infusion rates.

~~**Continuous Infusion**~~: DIPRIVAN Injection ~~0.1 to 0.2 mg/kg/min~~ administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection 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 injection higher rates of infusion are generally required (~~0.15 to 0.20 mg/kg/min~~) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

Reduce level of section subheading so it clearly indicates it is a section under **Maintenance of Anesthesia.**
Revise to: " ... 100 to 200 µg/kg/min ..."

Revise to: "... (150 to 200 µg/kg/min)"

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

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 Injection at rates higher than are clinically necessary. Generally, rates of ~~0.05 to 0.1 mg/kg/min~~ should be achieved during maintenance in order to optimize recovery times.

Revise to: " (50 to 100 µg/kg/min)"

~~**Intermittent Bolus**~~: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

Reduce level of section subheading so it clearly indicates it is a section under **Maintenance of Anesthesia.**

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and

nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

ADD new section with no indentation: **"Sedation for Monitored Anesthesia Care During Surgical and Diagnostic Procedures"**

ADD paragraphs: "When DIPRIVAN Injection is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients the rates of DIPRIVAN Injection administration will be approximately 50% of those used for maintenance of general anesthesia.

For initiation of sedation, either an infusion or a bolus dose method may be utilized. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injection at 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) and titrating to the desired level of sedation while closely monitoring respiratory function. With the bolus method for initiating sedation, patients will generally require 0.5 to 1.0 mg/kg titrated to clinical responses over 1 to 5 minutes.

For maintenance of sedation, either the variable rate or a bolus dose method can be utilized for titration to the desired level of sedation. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) titrated to desired level of sedation. During the infusion, bolus administration of 10 mg to 20 mg may be necessary if a rapid increase in sedation depth is required.

With the intermittent bolus dose method, increments of DIPRIVAN Injection 10 mg (1.0 mL) or 20 mg (2.0 mL) may be administered and titrated to desired level of sedation.

Although clinical data are limited, elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV may be more sensitive to the effects of sedative hypnotic agents. Therefore, the rate of administration and the dosage of DIPRIVAN Injection may need to be reduced (by approximately 30% to 50% of the usual sedative dose required for adults) in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE GUIDE.)"

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
~~**Induction**~~	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
~~**Maintenance**~~ **Infusion**	**Variable rate infusion**--titrated to the desired clinical effect. **Adults**: Generally, ~~0.1 to 0.2 mg/kg/min~~ (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, ~~0.05 to 0.1 mg/kg/min~~ (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Revise to: **"Induction of Anesthesia"**

Revise to: **"Maintenance of Anesthesia"**

Revise to: " 100 to 200 µg/kg/min"

Revise to: " 50 to 100 µg/kg/min"

ADD Sedation section to DOSAGE GUIDE:

INDICATION	DOSAGE AND ADMINISTRATION
Sedation	**Dosage and rate should be individualized.** **Adults:** Revise to: "For initiation, patients are likely to require an infusion of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) or a slow bolus of 0.5 to 1.0 mg/kg over 1 to 5 minutes. For maintenance, patients are likely to require an infusion of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** These patients are generally more sensitive, and dosages and rates of administration should be reduced by 30% to 50%.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, 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 Into a Running IV Catheter : Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- 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: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion.

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

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed

within 6 hours after the ampules or vials have been opened.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection, reservoirs, IV lines or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Aseptic Technique* for Handling DIPRIVAN Injection Ampules

- Wear clean garments.
- Wash hands and fingernails using an antimicrobial handwash.
- When appropriate, wear sterile gloves, mask and hair cover.
- Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry.
- Protect fingers and hands by using sterile gauze when opening the ampule.
- Withdraw DIPRIVAN Injection into a sterile syringe.
- Immediately replace needle cap and discard ampule.
- Label syringe with appropriate information, including date, time and patient name.
- Administer promptly.
- Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours -- whichever occurs sooner.

Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices)

- Wear clean garments.
- Wash hands and fingernails using an antimicrobial handwash.

- When appropriate, wear sterile gloves, mask and hair cover.

- Remove metal cap from vial.

- Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry.

- Insert sterile vent spike through rubber stopper and remove luer cap.

- Connect a sterile syringe(s) to vent spike and withdraw entire contents; (Or when using volumetric infusion devices, aseptically connect IV line to vent spike).

- Immediately cap syringe(s) with sterile closure(s) and discard vial and vent spike.

- Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time and patient name.

- Administer promptly.

- Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours -- whichever occurs sooner.

*These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products.

HOW SUPPLIED

DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol.

20 mL ampules (NDC 0038-0290-20)
50 mL infusion vials (NDC 0038-0290-50)

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

Made in Sweden
Manufactured for:
Stuart Pharmaceuticals
A business unit of ICI Americas Inc.
Wilmington, DE 19897 USA

~~SIC-64022-04~~ ~~Rev-D--02/91~~

~~DIPNO18.WP~~

Revise to: REV H 06/91

3colcopy.n17
DIPRIVAN DISK3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-002

MEDICAL REVIEW

201 JAN 19 1991

NDA 19-627 Date Completed: 19 December 1990

CLINICAL REVIEW & EVALUATION OF LABELING and BACKGROUND INFORMATION

PRODUCT: DIPRIVAN^{R} (propofol) Injection

SPONSOR: ICI Pharmaceuticals Group

DATE OF SUBMISSIONS: The two (2) submissions under review are both dated 13 December 1990.

CLINICAL SUMMARY:

The submissions under review continue the application to market 50 ml & 100 ml single patient infusion kits of DIPRIVAN^{R}. All that remains is the development of mutually agreeable labeling.

There are two microbiological studies for review. I have also been asked to render an opinion as to the usage of Diprivan^{R} by continuous infusion for prolonged surgery; particularly, I have been asked to render an opinion as to the time after opening that is necessary for use of Diprivan^{R} to be pragmatic in long surgical procedures.

I. Microbiology Study I, "Evaluation of Aseptic Handling Procedures"

A study was undertaken in an operating room atmosphere. Under recommended conditions, Diprivan^{R} was withdrawn from vials into syringes. A total of 2,040 cultures were taken from the syringes at 4, 6, 8 & 12 hours after withdrawal. The culture from one syringe was positive for staph. aureus at 6 hours; later cultures were taken from the same syringe 8 & 12 hours and these did not culture microrganisms. The culture from another syringe was positive for a gram positive rod at 8 hours. The organism could not be identified because there was no growth on subculture. A later culture was taken from the same syringe at 12 hours and there was no growth of microrganisms.

This culture rate is thus 0.098% or 2 positive cultures out of 2,040. The sponsor believes that this is within expected error range secondary to laboratory background contamination. The subsequent negative cultures from the same syringe (no growth) support their point of view. I have been reliably informed (H. Behrans, oral communication) that an HFD-160 Staff Microbiologist agrees.

Therefore, clinically significant microbiological contamination appears unlikely during the first 12 hours after withdrawal of Diprivan^{R} into a syringe, provided that standard aseptic technique is maintained.

II. Microbiology Study II, "Microbiology Challenge Tests"

This study is in technical microbiological language, unfamiliar to me. Therefore, definitive verification of the sponsor's conclusions will have to come from some person, or persons, other than me.

Diprivan^R was artificially contaminated with staph. aureus, candida albicans, E. coli & acinetobacter anitratus. The first three were tested based on adverse experience data; acinetobacter anitratus was selected because the similar moraxella osloensis, a subject of reports, could not be obtained in time.

The sponsor judges that there was no significant increase in viable count in Diprivan^R within 6 hours post contamination. "The conclusion from this limited study and from a literature search was that growth of micro-organisms in 'Diprivan' or any liquid emulsion, following touch contamination levels of inoculation, is unlikely to exceed a 1 $\log_{10}$ (10-fold) increase in viable count within 6 hours unless the micro-organisms have previously adapted to grow in the product."

The sponsor's conclusion requires verification by someone versed in the technical language unique for microbiology research.

III. DIPRIVAN^R for long surgical procedures.

Diprivan^R was studied and found to be safe and effective if used along with nitrous oxide-oxygen for maintenance of general anesthesia in short surgical procedures, such as gynecological dilation & currettage. Based upon pharmacokinetic data, not clinical studies, the drug was approved for longer surgical procedures without restriction as to time. Although the elimination half-life ranges from 300-700 minutes, Diprivan^R has a high metabolic clearance, exceeding estimates of hepatic blood flow. Thus, the plasma level is low despite significant storage during the slow phase in less well perfused tissues.

The sponsor now proposes, out of microbiological considerations, to limit use to the first 8 hours after removal by syringe.

The pharmacokinetic data made it appear reasonable to go beyond the time limit of short surgical procedures, despite the fact that clinical data were lacking for longer procedures. Pending microbiological verification, there still appears to be no reason to restrict use during the first 6 hours after opening. After 6 hours, it can be presumed that open surgical wounds are contaminated, at best; it would be difficult to differentiate the cause of an infection. Diprivan^{R} lowers blood pressure more than most anesthetic agents, making it quit trying during prolonged surgery for an anesthetist to make repeated clinical judgements as to when this is beneficial to the patient, or at least neutral; after 4, 6 or 8 hours, depending on how well rested the person was, fatigue would set in.

The longer the case, the less clinical experience we have with use of Diprivan^{R} as the primary agent to supplement nitrous oxide. The strongest support for use of Diprivan^{R} comes from those advocates who believe that use of Diprivan^{R} promotes faster recovery from general anesthesia in ambulatory (day care) patients. Patients who require prolonged surgery are, probably in direct porportion to the length of surgery, less likely to be sent home on the day of surgery. Other agents (enflurane, isoflurane, narcotics, thiobarbiturates, benzodiazepines, alone or in combination) are available, and perhaps better suited, for surgery lasting more than 6 hours.

Recommending 6 hours of use is, unfortunately, arbitrary; however, so is recommending 8 hours of use. If given a choice between the two arbitrary designations, I would recommend that Diprivan^{R} be discarded after 6 hours. If the anesthetist judges that continued use of Diprivan^{R} is indicated, another sterile ampul or vial could still be opened.

RECOMMENDATIONS (REVIEW OF LABELING):

I endorse the sponsor's draft package insert submitted on 13 December 1990, except that wherever the recommendation is made to discard Diprivan^{R} "..within 8 hours..." this should be changed to "...within 6 hours...". These recommendations are made in the **Handling Procedures** sub-section of DOSAGE AND ADMINISTRATION.

I endorse the final printed paper carton and immediate container labeling submitted on 13 December 1990 except that wherever "..within 8 hours..." appears it should be changed to "...within 6 hours...".

David L. Scally, M.D.

David L. Scally

0202d, dls/DLS

Concur: Rm. W Duncan

12-19-90

20.1

JAN 11 1991

NDA 19-627 Date Completed: 11 January 1991

CLINICAL REVIEW & EVALUATION OF LABELING

Product: DIPRIVAN^{R} (propofol) Injection
ICI of Wilmington, Delaware

Date of Submission: 28 December 1990
Known variously as SLR-005 &/or 002, SLR

Purpopse: Revise container labeling for 20 ml ampules of 1% Diprivan^{R} to maintain consistency with recent safety changes tailored for the soon to be introduced larger volume containers (50 & 100 ml).

SUMMARY, CONCLUSION & RECOMMENDATION:

The final printed packaging labeling, and prescription drug labeling (package insert), contained in the submission dated 28 December 1990 is clinically acceptable and should be approved.

David L. Scally, M.D.

0208d
dls,DLS
11 JAN MCMXCI

NDA 19-627 Date Completed: 11 January 1991

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David L. Scally

David L. Scally, M.D.

0208d
dls,DLS
11 JAN MCMXCI

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627 / S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

SE1-002

Pharmaceuticals Group

Stuart Pharmaceuticals/ICI Pharma

COPY 1

HAND DELIVERED

July 2, 1991

NDA SUPPL AMENDMENT

CENTER FOR DRUG REC'D JUL 02 1991 HFD-007 EVALUATION AND RESEARCH

ICI Pharmaceuticals Group
Wilmington
Delaware 19897 USA

Dr. David L. Scally
Pilot Drug Evaluation Staff
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 007, Room No. 9B-23
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Scally:

Re: DIPRIVAN® (propofol)
NDA 19-627

Enclosed, per your request, are the following documents:

1. The proposed label to reflect the inclusion of Sedation During Monitored Anesthesia Care.

2. The data supplied to Dr. Carol Lake to assist her in her review regarding repeat bolus dosing (Dr. Pratilla's study) and the Abstract from that study.

3. A copy of the current bibliography regarding the use of DIPRIVAN® (propofol) and Sedation During Monitored Anesthesia Care.

4. The publications from the Camu/Gepts study are enclosed. Since this study is a pharmacokinetics study, it was reviewed and presented by Dr. Donald Stansky during the NDA Day apart from the rest of the clinical package. A 3-page synopsis was, therefore, not generated.

If I can be of any further assistance, please do not hesitate to contact me.

Sincerely,

Nanette E. Holston
Assistant Manager, Drug Registration
Drug Regulatory Affairs Department
(302) 886-8980

NEH/jr
Enclosures

11/20/91 Noted
S. Schmidt