PDR®

51 EDITION

1997

PHYSICIANS' DESK REFERENCE®

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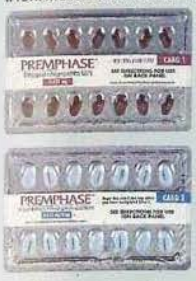
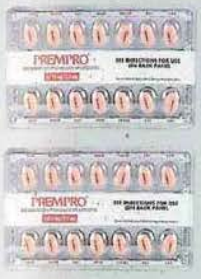
ISBN: 1-56363-201-2

RX WYETH-AYERST LABORATORIES P. 2900



Premphase®
(conjugated estrogens tablets/ medroxyprogesterone acetate tablets, USP)
0.625 mg / 5.0 mg

RX WYETH-AYERST LABORATORIES P. 2905



Prempro™
(conjugated estrogens tablets/ medroxyprogesterone acetate tablets, USP)
0.625 mg / 2.5 mg

RX WYETH-AYERST LABORATORIES P. 2911

904* 15 mg

Redux®
(dexfenfluramine)

RX WYETH-AYERST LABORATORIES P. 2914

4177* 200 mg

4179* 400 mg

††Sectral®
(acebutolol HCl)

C-IV WYETH-AYERST LABORATORIES P. 2916

317* 15 mg

††Serax®
(oxazepam)

C-IV WYETH-AYERST LABORATORIES P. 2916

51* 10 mg

6* 15 mg

52* 30 mg

††Serax®
(oxazepam)

RX WYETH-AYERST LABORATORIES P. 2917

4132* 25 mg

4133* 50 mg

4158* 100 mg

†Surmontil®
(trimipramine maleate)

RX WYETH-AYERST LABORATORIES P. 2932

559* 250 mg

560* 500 mg

†Wymox®
(amoxicillin)

C-IV WYETH-AYERST LABORATORIES P. 2930

85**

Wygesic®
(propoxyphene HCl, USP, acetaminophen, USP)
65 mg /650 mg

RX WYETH-AYERST LABORATORIES P. 2919

641** 642** 643**

2535*

Triphasil®-21
(21 tablets containing the following: 6 brown tablets - 0.050 mg levonorgestrel + 0.030 mg ethinyl estradiol; 5 white tablets - 0.075 mg levonorgestrel + 0.040 mg ethinyl estradiol; 10 light-yellow tablets - 0.125 mg levonorgestrel + 0.030 mg ethinyl estradiol)

RX WYETH-AYERST LABORATORIES P. 2924

641** 642** 643** 650**

2536*

Triphasil®-28
(28 tablets containing the following: 6 brown tablets - 0.050 mg levonorgestrel + 0.030 mg ethinyl estradiol; 5 white tablets - 0.075 mg levonorgestrel + 0.040 mg ethinyl estradiol; 10 light-yellow tablets - 0.125 mg levonorgestrel + 0.030 mg ethinyl estradiol; 7 light-green inert tablets)

RX WYETH-AYERST LABORATORIES P. 2924

641** 642** 643** 650**

Clinic Pilpak®

Triphasil®-28
(28 tablets containing the following: 6 brown tablets - 0.050 mg levonorgestrel + 0.030 mg ethinyl estradiol; 5 white tablets - 0.075 mg levonorgestrel + 0.040 mg ethinyl estradiol; 10 light-yellow tablets - 0.125 mg levonorgestrel + 0.030 mg ethinyl estradiol; 7 light-green inert tablets)

ZENECA PHARMACEUTICALS

RX ZENECA PHARMACEUTICALS P. 2932

1 mg

Arimidex®
(anastrozole)

RX ZENECA PHARMACEUTICALS P. 2936

1 g/10 mL vial

2 g/20 mL vial

10 g per bulk pharmacy package

1 g/100 mL vial

2 g/100 mL vial

Cefotan® IM/IV
(sterile cefotetan disodium)

RX ZENECA PHARMACEUTICALS P. 2934

50 mg

Casodex®
(bicalutamide)

RX ZENECA PHARMACEUTICALS P. 2939

10 mg/mL per 50 mL vial

10 mg/mL per 20 mL ampules

10 mg/mL per 100 mL vial

Diprivan®
(propofol)

RX ZENECA PHARMACEUTICALS P. 2945

10 mg 25 mg 50 mg

75 mg 100 mg

150 mg

Elavil®
(amitriptyline HCl)

OTC ZENECA PHARMACEUTICALS P. 2947

22 mL
Sponge/Brush with nail cleaner

Hibiclens®
(chlorhexidine gluconate)

RX WYETH-AYERST LABORATORIES P. 2926

Tubex® Injector and Sterile Cartridge-Needle Unit with hard cannula cover ready for injection.

Tubex® Blunt Pointe™ Sterile Cartridge-Needle Unit for use in selected "needle-less" IV port systems*

*(*Consult product prescribing information for compatibility information in the Product Information section of this PDR.)*

Tubex® Closed Injection System

Examples of Tubex® Sterile Cartridge-Needle Units, Tubex® Blunt Pointe™ Sterile Cartridge-Unit, and Tubex® Injector, components of the Tubex Closed Injection System, the most comprehensive line of small-volume unit-dose prefilled syringe injectibles. For complete list of products available, consult Tubex listing in the Product Information Section.

While every effort has been made to reproduce products faithfully, this section is to be considered a quick reference identification aid. In cases of suspected overdosage, etc., chemical analysis of the product should be done.

† The appearance of these tablets and capsules is a trademark of Wyeth-Ayerst Laboratories
**Product identification number on reverse side

Δ The appearance of these tablets and capsules is a registered trademark of Wyeth-Ayerst Laboratories.

Intravenous Administration:
The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.
For intermittent intravenous administration, a solution containing 1 gram or 2 grams of CEFOTAN (cefotetan disodium for injection) in Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, the solution may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN (cefotetan disodium for injection), it is advisable to discontinue temporarily the administration of other solutions at the same site.
NOTE: Solutions of CEFOTAN must not be admixed with solutions containing aminoglycosides. If CEFOTAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.
Intramuscular Administration:
As with all intramuscular preparations, (cefotetan disodium for injection) should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

CEFOTETAN INJECTION

Directions for Use of CEFOTAN (cefotetan injection) in Galaxy® Plastic Container (PL2040)
CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040) is for intravenous administration only.
Storage: Store in a freezer capable of maintaining a temperature of -20°C/-4°F.
Thawing of Plastic Container: Thaw frozen container at room temperature (25°C/77°F) or in a refrigerator (5°C/41°F).
[DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.]
Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.
The container should be visually inspected. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.
Preparation of Intravenous Use (Use aseptic technique):
1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.
Intravenous Administration:
The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.
Using an infusion system, CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040) should be given over 20 to 60 minutes through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040), it is advisable to discontinue temporarily the administration of other solutions at the same site.
Compatibility and Stability of CEFOTAN Products:
Frozen samples should be thawed at room temperature before use. After the periods mentioned below, any unused solutions or frozen material should be discarded. **DO NOT REFREEZE.**
NOTE: Solutions of CEFOTAN must not be admixed-with solutions containing aminoglycosides. If CEFOTAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection. **DO NOT ADD SUPPLEMENTARY MEDICATION.**

CEFOTETAN DISODIUM FOR INJECTION

CEFOTAN (cefotetan disodium for injection) reconstituted as described above (PREPARATION OF SOLUTION) maintains satisfactory potency for 24 hours at room temperature (25°C/77°F), for 96 hours under refrigeration (5°C/41°F), and for at least 1 week in the frozen state (-20°C/-4°F). After reconstitution and subsequent storage in disposable glass or plastic syringes, CEFOTAN (cefotetan disodium for injection) is stable for 24 hours at room temperature and 96 hours under refrigeration.
ADD-Vantage Vials:
Ordinarily, ADD-Vantage Vials should be reconstituted only when it is certain that the patient is ready to receive the drug. However, ADD-Vantage Vials of CEFOTAN reconstituted as described in Preparation of Solution, for ADD-Vantage Vials, maintains satisfactory potency for 24 hours at room temperature (25°C/77°F).
(DO NOT REFRIGERATE OR FREEZE CEFOTAN IN ADD-VANTAGE VIALS.)

CEFOTETAN INJECTION

The thawed solution in Galaxy® plastic container (PL 2040) remains chemically stable for 48 hours at room temperature (25°C/77°F) or for 21 days under refrigeration (5°C/41°F).
NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

CEFOTAN (cefotetan disodium for injection) is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The vials should not be stored at temperatures above 22° C (72° F) and should be protected from light.
1 g ADD-Vantage Vial (NDC 0310-0376-31)
2 g ADD-Vantage Vial (NDC 0310-0377-32)
1 g Vial (NDC 0310-0376-10)
2 g Vial (NDC 0310-0377-20)
1 g Piggyback Vial (NDC 0310-0376-11)
2 g Piggyback Vial (NDC 0310-0377-21)
CEFOTAN is also available as a 10 g pharmacy bulk package.
10g in 100 mL Vial (NDC 0310-0375-10)
CEFOTAN (cefotetan injection) is supplied as a frozen, isosmotic, premixed solution in single dose Galaxy® plastic containers (PL 2040) as follows:
1 g in 50 mL plastic container (NDC 0310-0378-51)
2 g in 50 mL plastic container (NDC 0310-0379-51)
Store containers at or below -20°C/-4°F. **[See DIRECTIONS FOR USE OF CEFOTAN (cefotetan injection) IN GALAXY® PLASTIC CONTAINER (PL 2040)].**

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.
3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria—Third Edition. Approved Standard NCCLS Document M11-A3, Vol 13, No. 26, NCCLS, Villanova, PA, December 1993.

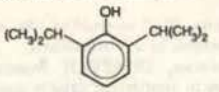
*Galaxy® is a registered trademark of Baxter Healthcare Corporation.
†ADD-Vantage is a registered trademark of Abbott Laboratories Inc.
‡ Clinitest® is a registered trademark of Ames Division, Miles Laboratories, Inc.
CEFOTAN® (cefotetan injection) in Galaxy® plastic container (PL 2040) is manufactured by Baxter Healthcare Corporation, Deerfield, Illinois 60015 USA for Zeneca Pharmaceuticals.
CEFOTAN® (cefotetan disodium for injection) is manufactured by SmithKline Beecham Corporation for:
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5437
Rev E 1/96 SIC 64065-01

Shown in Product Identification Guide, page 341

DIPRIVAN® 1% ℞
INJECTABLE EMULSION
10 mg/mL propofol
FOR I.V. ADMINISTRATION
Formerly DIPRIVAN® (propofol) Injection
PROFESSIONAL INFORMATION BROCHURE

DESCRIPTION

DIPRIVAN® Injectable Emulsion 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 structural and molecular 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 pKa is 11. The octanol/water partition coefficient for propofol 6761:1 at a pH of 6-8.5. 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 is isotonic and has a pH of 7-8.5.
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 RETARD THE RATE OF GROWTH OF MICROORGANISMS 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.

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 produces hypnosis rapidly with minimal excitation, usually within 40 seconds from the start of an 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, and this accounts for the rapid induction of anesthesia.
Pharmacodynamics
Pharmacodynamic properties of propofol are dependent upon the therapeutic blood propofol concentrations. Steady state propofol blood concentrations are generally proportional to infusion rates, especially within an individual patient. Undesirable side effects such as cardiorespiratory depression are likely to occur at higher blood concentrations which result from bolus dosing or rapid increase in infusion rate. An adequate interval (3 to 5 minutes) must be allowed between clinical dosage adjustments in order to assess drug effects.
The hemodynamic effects of DIPRIVAN Injectable Emulsion 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 (e.g., fentanyl) when 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 IV induction agents traditionally used for this purpose.
Clinical and preclinical studies suggest that DIPRIVAN Injectable Emulsion is rarely associated with elevation of plasma histamine levels.
Induction of anesthesia with DIPRIVAN Injectable Emulsion is frequently associated with apnea in both adults and children. In 1573 adult patients who received DIPRIVAN Injectable Emulsion (2 to 2.5 mg/kg); apnea lasted less than 30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. In the 213 pediatric patients between the ages of 3 and 12 years assessable for apnea who received DIPRIVAN Injectable Emulsion (1 to 3.6 mg/kg), apnea lasted less than 30 seconds

Continued on next page

Zeneca Pharmaceuticals—Cont.

in 12% of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

During maintenance, DIPRIVAN Injectable Emulsion 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 (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, airway obstruction, and/or oxygen desaturation 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, and 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 III/IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) DIPRIVAN Injectable Emulsion is not recommended for MAC Sedation in children because safety and effectiveness have not been established.

Clinical studies in humans and studies in animals show that DIPRIVAN Injectable Emulsion does not suppress the adrenal response to ACTH. Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injectable Emulsion 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 Injectable Emulsion to induce malignant hyperthermia.

Studies to date 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).

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 is unknown.

Pharmacokinetics

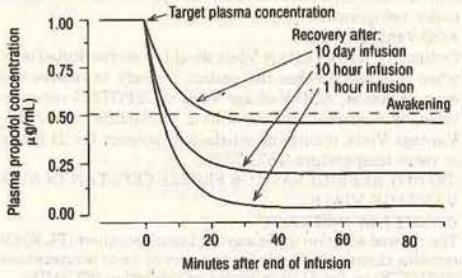
The proper use of DIPRIVAN Injectable Emulsion requires an understanding of the disposition and elimination characteristics of propofol.

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 highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high 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 will occur even after long term administration. If, however, higher than necessary infusion levels have been maintained for a long time, propofol will be redistributed from fat and muscle to the plasma, and this return of propofol from peripheral tissues will slow recovery.

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



The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions (at steady state), about half the initial rate will maintain the same plasma levels. 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 of long duration.

Adults: Propofol clearance ranges from 23-50 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 endpoint (dose-requirement) decreases. This does not appear to be an age-related change of 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 oxygen desaturation. The higher plasma levels reflect an age-related decrease in volume of distribution and reduced intercompartmental clearance. Lower doses are thus recommended for initiation and maintenance of sedation/anesthesia in elderly patients. (See CLINICAL PHARMACOLOGY—Individualization of Dosage.)

Pediatrics: The pharmacokinetics of propofol were studied in 53 children between the ages of 3 and 12 years who received DIPRIVAN Injectable Emulsion for periods of approximately 1–2 hours. The observed distribution and clearance of propofol in these children was 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

DIPRIVAN Injectable Emulsion was compared to intravenous and inhalational anesthetic or sedative agents in 91 trials involving a total of 5,135 patients. Of these 3,354 received DIPRIVAN Injectable Emulsion and comprised the overall safety database for anesthesia and MAC sedation. Fifty-five of these trials, 20 for anesthesia induction and 35 for induction and maintenance of anesthesia or MAC sedation, were carried out in the US or Canada and provided the basis for dosage recommendations and the adverse event profile during anesthesia or MAC sedation.

Pediatric Anesthesia

DIPRIVAN Injectable Emulsion was compared to standard anesthetic agents in 12 clinical trials involving 534 patients receiving DIPRIVAN Injectable Emulsion. Of these, 349 were from US/Canadian clinical trials and comprised the overall safety database for Pediatric Anesthesia.

TABLE 1. PEDIATRIC ANESTHESIA CLINICAL TRIALS
Patients Receiving DIPRIVAN Injectable Emulsion
Median and (Range)

	Induction Only	Induction and Maintenance
Number of Patients*	243	105
Induction Bolus Dosages	2.5 mg/kg (1–3.5)	3 mg/kg (2–3.6)
Injection Duration	20 sec (6–45)	
Maintenance Dosage	—	181 μg/kg/min (107–418)
Maintenance Duration	—	78 min (29–268)

*Body weight not recorded for one patient.

Neuroanesthesia

DIPRIVAN Injectable Emulsion was studied in 50 patients undergoing craniotomy for supratentorial tumors in two clinical trials. The mean lesion size (anterior/posterior and lateral) was 31 mm and 32 mm in one trial and 55 mm and 42 mm in the other trial respectively. [See Table 2 below.] In ten of these patients, DIPRIVAN Injectable Emulsion was administered by infusion in a controlled clinical trial to evaluate the effect of DIPRIVAN Injectable Emulsion 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), whereas the percent change in cerebrospinal fluid pressure (CSFP) was -46% ± 14%. As CSFP is an indirect measure of intracranial pressure (ICP), when given by infusion or slow bolus, DIPRIVAN Injectable Emulsion, in combination with hypocarbia, is capable of decreasing ICP independent of changes in arterial pressure.

Intensive Care Unit (ICU) Sedation

DIPRIVAN Injectable Emulsion was compared to benzodiazepines and/or opioids in 14 clinical trials involving a total of 550 ICU patients. Of these, 302 received DIPRIVAN Injectable Emulsion and comprise the overall safety database for ICU sedation. Six of these studies were carried out in the US or Canada and provide the basis for dosage recommendations and the adverse event profile.

Information from 193 literature reports of DIPRIVAN Injectable Emulsion used for ICU sedation in over 950 patients and information from the clinical trials are summarized below: [See Table 3 at top of next page.]

Cardiac Anesthesia

DIPRIVAN Injectable Emulsion was evaluated in 5 clinical trials conducted in the US and Canada, involving a total of 569 patients undergoing coronary artery bypass graft (CABG). Of these, 301 patients received DIPRIVAN Injectable Emulsion. They comprise the safety database for cardiac anesthesia and provide the basis for dosage recommendations in this patient population, in conjunction with reports in the published literature.

Individualization of Dosage

General: 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 RETARD THE RATE OF GROWTH OF MICROORGANISMS 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.

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 clinical dosage adjustments in order to assess drug effects.

When administering DIPRIVAN Injectable Emulsion by infusion, syringe pumps 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 (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 Injectable Emulsion 25 mg (2.5 mL) to 50 mg (5 mL) incremental boluses and/or by increasing the infusion rate.

TABLE 2. NEUROANESTHESIA CLINICAL TRIALS
Patients Receiving DIPRIVAN Injectable Emulsion Median and (Range)

Patient Type	No. of Patients	Induction Bolus Dosages (mg/kg)	Maintenance Dosage (μg/kg/min)	Maintenance Duration (min)
Craniotomy patients	50	1.36 (0.9–6.9)	146 (68–425)	285 (48–622)

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