CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

Approval Letter

ANDA 75-102

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
17 Hughes
Irvine, CA 92618

JAN 4 1999

Dear Madam:

This is in reference to your abbreviated new drug application dated March 31, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Propofol Injectable Emulsion 1% (10 mg/mL).

Reference is also made to your amendments dated May 20, and December 3, 1997; and January 16, February 11, March 12, April 13, May 27, August 24, October 16, November 10, December 14, December 15, December 21, and December 28, 1998.

The listed drug referenced in your application is subject to a period of patent protection which expires on March 22, 2015 (patents 5,714,520 [the '520 patent], 5,731,355 and 5,731,356). Your application contains certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on any of the listed patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of this application shall be made effective immediately unless an action is brought for infringement of one or more of the patents which are the subject of the certifications before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that Zeneca Limited initiated a patent infringement suit within the forty-five day period involving the '520 patent in the United States District Court for the District of Delaware (Zeneca Limited v. Gensia Sicor Pharmaceuticals, Inc. [Civil Action No. 98-170 (JJF)]). You have also notified the Agency that on April 17, 1998, Zeneca Limited dismissed the suit against Gensia Sicor Pharmaceuticals, Inc. without prejudice.

The listed drug referenced in your application is also subject to a period of new product (NP) market exclusivity expiring on June 11, 1999, for Propofol Injectable Emulsion, 10 mg/mL, formulated with EDTA as a preservative. As the drug product provided for in the current abbreviated new drug application is formulated using sodium metabisulfite as the preservative in place of EDTA, you have informed the Agency that the current exclusivity is not applicable to your drug product.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Propofol Injectable Emulsion 1% (10 mg/mL) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diprivan Injectable Emulsion 1% of Zeneca Ltd.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 1/4/99

Róger L. Williams, M.D.
Deputy Center Director for Pharmacuetical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

FINAL PRINTED LABELING

Y36-204-201
Package Insert

GensiaSicor™ PHARMACEUTICALS

Propofol

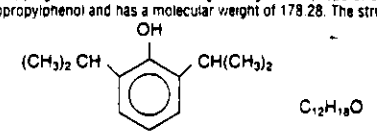
Injectable Emulsion 1%
200 mg/20 mL (10 mg/mL) propofol

Contains a Sulfite

For I.V. Administration

DESCRIPTION

Propofol 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 178.28. 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 is 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 yolk phospholipid (12 mg/mL), and sodium metabisulfite (0.25 mg/mL); with sodium hydroxide to adjust pH. The propofol injectable emulsion is isotonic and has a pH of 4.5-6.4.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS SODIUM METABISULFITE (0.25 mg/mL) TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL 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 PROPOFOL 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

Propofol 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 propofol 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 propofol, 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 propofol 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 propofol is rarely associated with elevation of plasma histamine levels.

Induction of anesthesia with propofol is frequently associated with apnea in both adults and children. In 1573 adult patients who received propofol (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 propofol (1 to 3.6 mg/kg), apnea lasted less than 30 seconds in 12% of patients, 30-60 seconds in 10% of patients, and more than 60 seconds in 5% of patients.

During maintenance, propofol 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 propofol. Hypotension, oxyhemoglobin desaturation, apnea, airway obstruction, and/or oxygen desaturation can occur, especially following a rapid bolus of propofol. 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.) Propofol 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 propofol does not suppress the adrenal response to ACTH.

Preliminary findings in patients with normal intraocular pressure indicate that propofol 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 propofol to induce malignant hyperthermia.

Studies to date indicate that propofol when used in combination with hypocarbia increases cerebrovascular resistance and decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure. Propofol does not affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. (See Clinical Trials - Neuroanesthesia.)

Pharmacokinetics

The proper use of propofol 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.

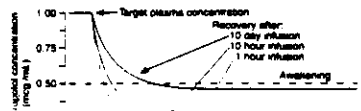
Following an I.V. bolus dose, there is a rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both rapid distribution and high metabolic clearance. Distribution accounts 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 propofol 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 propofol 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.



[illegible] dose administration should not be used for MAC sedation. (See WARNINGS - Propofol is not recommended for MAC sedation in children because safety and effectiveness have not been established)

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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.

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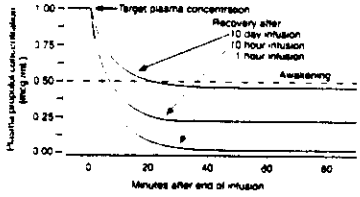

The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions (at steady state), about half the initial rate will maintain the same plasma levels. Failure to reduce the infusion rate in patients receiving propofol 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 propofol 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 end point (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 I.V. 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 propofol for periods of approximately 1-2 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

Propofol 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 propofol 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

Propofol was compared to standard anesthetic agents in 12 clinical trials involving 534 patients receiving propofol. 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 Propofol 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 mcg/kg/min (107-418)
Maintenance Duration	-	78 min (29-268)

*Body weight not recorded for one patient.

Neuroanesthesia

Propofol 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.

TABLE 2. NEUROANESTHESIA CLINICAL TRIALS
Patients Receiving Propofol Median and (Range)

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

In ten of these patients, propofol was administered by infusion in a controlled clinical trial to evaluate the effect of propofol 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, propofol, in combination with hypocarbia, is capable of decreasing ICP independent of changes in arterial pressure.

Intensive Care Unit (ICU) Sedation

Propofol was compared to benzodiazepines and/or opioids in 14 clinical trials involving a total of 550 ICU patients. Of these, 302 received propofol 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 propofol used for ICU sedation in over 950 patients and information from the clinical trials are summarized below:

TABLE 3. ICU SEDATION CLINICAL TRIALS AND LITERATURE
Patients Receiving Propofol Median and (Range)

ICU Patient Type	Number of Patients Trials	Number of Patients Literature	Sedation Dose mcg/kg/min	Sedation Dose mg/kg/h	Sedation Duration Hours
Post-CABG	41	-	11 (0.1-30)	0.66 (0.006-1.8)	10 (2-14)
Post-Surgical	-	334	(5-100)	(0.3-6)	(4-24)
	60	-	20 (6-53)	1.2 (0.4-3.2)	18 (0.3-187)
Neuro/Head Trauma	-	142	(23-82)	(1.4-4.9)	(6-96)
	7	-	25 (13-37)	1.5 (0.8-2.2)	168 (112-282)
Medical	-	184	(8.3-87)	(0.5-5.2)	(8 hr-5 days)
	49	-	41 (9-131)	2.5 (0.5-7.9)	72 (0.4-337)
	-	76	(3.3-62)	(0.2-3.7)	(4-96)
Special Patients					
ARDS/Resp. Failure	-	56	(10-142)	(0.6-8.5)	(1 hr-8 days)
COPD/Asthma	-	49	(17-75)	(1-4.5)	(1-8 days)
Status Epilepticus	-	15	(25-167)	(1.5-10)	(1-21 days)
Tetanus	-	11	(5-100)	(0.3-6)	(1-25 days)

Trials (Individual patients from clinical studies)
Literature (Individual patients from published reports)
CABG (Coronary Artery Bypass Graft)
ARDS (Adult Respiratory Distress Syndrome)

Cardiac Anesthesia

Propofol 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 propofol. 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. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS SODIUM METABISULFITE (0.25 mg/mL) TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL 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 PROPOFOL 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 propofol by infusion, syringe pumps or volumetric pumps are recommended to provide controlled infusion rates. When infusing propofol 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 propofol 25 mg (2.5 mL) to 50 mg (5 mL) incremental boluses and/or by increasing the infusion rate.

For minor surgical procedures (e.g., body surface), nitrous oxide (60%-70%) can be combined with a variable rate propofol 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 propofol 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 propofol 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 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 ASA I/II require 2 to 2.5 mg/kg of propofol for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, propofol 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 propofol.

Elderly, Debilitated, or ASA III/IV Patients: It is important to be familiar and experienced with the intravenous use of propofol before treating elderly, debilitated, or ASA III/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 propofol 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.

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Elderly, Debilitated, or ASA III/IV Patients: It is important to be familiar and experienced with the intravenous use of propofol before treating elderly, debilitated, or ASA III/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 propofol 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.)

Neurosurgical Patients: Slower induction is recommended using boluses of 20 mg every 10 seconds. Slower boluses or infusions of propofol 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: Propofol 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, propofol 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 propofol, 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, propofol 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 propofol maintenance infusion rates and therapeutic blood concentrations when compared to non-narcotic (lorazepam) premedication. The rate of propofol 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 propofol 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, propofol maintenance rates should not be less than 50 mcg/kg/min; and care should be taken to ensure amnesia with concomitant benzodiazepines. Higher doses of propofol will reduce the opioid requirements. (See Table 4.) When propofol 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)
Propofol		OPIOID[a]/0.05-0.075 mcg/kg/min (no bolus)
Preinduction anxiolysis	25 mcg/kg/min	
Induction	0.5-1.5 mg/kg over 60 sec	
Maintenance (Titrated to Clinical Response)	100-150 mcg/kg/min	
OPIOID[b]		Propofol 50-100 mcg/kg/min (no bolus)
Induction	25-50 mcg/kg	
Maintenance	0.2-0.3 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 with concomitant benzodiazepine therapy

Maintenance of General Anesthesia

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

Continuous Infusion: Propofol 100 to 200 mcg/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 propofol 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%-50% during the first half-hour of maintenance.

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

Intermittent Bolus: Increments of propofol 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.

Propofol 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 III/IV patients, rapid bolus doses should not be used as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

Pediatric Anesthesia:

Induction of General Anesthesia: Most pediatric patients 3 years of age or older and classified ASA I or II require 2.5 to 3.5 mg/kg of propofol for induction when unpremedicated or when lightly premedicated with oral benzodiazepines or intramuscular opioids. Within this dosage range, younger children may require larger induction doses than older children. 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 propofol. In addition, a lower dosage is recommended for children ASA III or IV. Attention should be paid to minimize pain on injection when administering propofol to pediatric patients. Rapid boluses of propofol may be administered if small veins are pretreated with lidocaine or when antecubital or larger veins are utilized. (See PRECAUTIONS - General.)

Propofol administered in a variable rate infusion with nitrous oxide 60%-70% provides satisfactory anesthesia for most pediatric patients 3 years of age or older, ASA I or II, undergoing general anesthesia.

Maintenance of General Anesthesia: Maintenance by infusion of propofol at a rate of 200-300 mcg/kg/min should immediately follow the induction dose. Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased; during this period, infusion rates of 125-150 mcg/kg/min are typically needed. However, younger children (5 years of age or less) may require larger maintenance infusion rates than older children.

Monitored Anesthesia Care (MAC) Sedation in Adults

When propofol is administered for MAC sedation, rates of administration should be individualized and titrated to clinical response. In most patients, the rates of propofol administration will be in the range of 25-75 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 III/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/or oxygen desaturation.**

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 propofol 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 level of sedation 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 propofol 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 III/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 3-5 minutes, and the dosage of propofol 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 propofol at rates higher than are clinically necessary.

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

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.) The rate of administration and the dosage of propofol 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.)

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

ICU Sedation: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.)

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.)

Across all 6 US/Canadian clinical studies, the mean infusion maintenance rate for all propofol 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). In these studies, morphine or fentanyl was used as needed for analgesia.

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.

Although there are reports of reduced analgesic requirements, most patients received opioids for analgesia during maintenance of ICU sedation. 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. (See Clinical Trials, Table 3.)

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 propofol required 35% less nitroprusside than midazolam patients; this difference was statistically significant ($P<0.05$). 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. (See Clinical Trials, Table 3.)

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

In hemodynamically stable head trauma patients ranging in age from 19-43 years, adequate sedation was maintained with propofol or morphine ($N=7$ in each group). There were no apparent differences in adequacy of sedation, intracranial pressure, cerebral perfusion pressure, or neurologic recovery between the treatment groups. In literature reports from Neurosurgical ICU and severely head-injured patients, propofol infusion, with or without diuretics and hyperventilation, controlled intracranial pressure while maintaining cerebral perfusion pressure. In some patients, bolus doses resulted in decreased blood pressure and compromised cerebral perfusion pressure. (See Clinical Trials, Table 3.)

Propofol 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. (See Clinical Trials, Table 3.)

Abrupt discontinuation of propofol 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 propofol should be adjusted to maintain a light level of sedation through the weaning process or evaluation of sedation level. (See PRECAUTIONS.)

INDICATIONS AND USAGE

Propofol injectable emulsion is an I.V. sedative-hypnotic 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 in adults and in children 3 years of age or older.

Propofol, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures in adults. Propofol may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.)

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

Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta; and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression. (See PRECAUTIONS.)

Propofol is not recommended for use in nursing mothers because propofol 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.)

Propofol is not recommended for anesthesia in children below the age of 3 years because safety and effectiveness have not been established. Propofol is not recommended for MAC sedation in children because safety and effectiveness have not been established. Propofol is not recommended for pediatric ICU sedation because safety and effectiveness have not been established.

CONTRAINDICATIONS

Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol injectable emulsion or its components, or when general anesthesia or sedation are contraindicated.

WARNINGS

Although there are reports of reduced analgesic requirements [illegible] tion. 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. (See Clinical Trials, Table 3.)

In post-CABG (coronary artery bypass graft) patients, the maintenance rate of propofol administration was usually low (median 17 mcg/kg/min) due to the intraoperative administration of high opioid doses. Patients receiving propofol required 35% less nitroprusside than midazolam patients; this difference was statistically significant ($P<0.05$). 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. (See Clinical Trials, Table 3.)

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

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Propofol 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. (See Clinical Trials, Table 3.)

Abrupt discontinuation of propofol 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 propofol should be adjusted to maintain a light level of sedation through the weaning process or evaluation of sedation level. (See PRECAUTIONS.)

INDICATIONS AND USAGE

Propofol injectable emulsion is an I.V. sedative-hypnotic 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 in adults and in children 3 years of age or older.

Propofol, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures in adults. Propofol may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.)

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

Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta; and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression. (See PRECAUTIONS.)

Propofol is not recommended for use in nursing mothers because propofol 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.)

Propofol is not recommended for anesthesia in children below the age of 3 years because safety and effectiveness have not been established. Propofol is not recommended for MAC sedation in children because safety and effectiveness have not been established. Propofol is not recommended for pediatric ICU sedation because safety and effectiveness have not been established.

CONTRAINDICATIONS

Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol injectable emulsion or its components, or when general anesthesia or sedation are contraindicated.

WARNINGS

For general anesthesia or monitored anesthesia care (MAC) sedation, propofol 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.

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

In the elderly, debilitated, or ASA III/IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

MAC sedation patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. 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 initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated, or ASA III/IV patients.

Propofol 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 is not known.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS SODIUM METABISULFITE (0.25 mg/mL) TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL 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 PROPOFOL INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

PRECAUTIONS

General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated, or ASA III/IV patients. (See CLINICAL PHARMACOLOGY - Individualization of Dosage.) 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 propofol injectable emulsion is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist.

When propofol is administered to an epileptic patient, there may be a risk of seizure during the recovery phase.

In adults and children, attention should be paid to minimize pain on administration of propofol. 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 I.V. 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.

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 observed up to 14 days following induction. 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. 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 postmarketing period there have been rare reports of local pain, swelling, blisters, and/or tissue necrosis following accidental extravasation of propofol injectable emulsion.

Perioperative myoclonia, rarely including convulsions and opisthotonos, has occurred in temporal relationship in cases in which propofol has been administered.

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

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

Propofol has no vagolytic activity. Reports of bradycardia, asystole, and, rarely, cardiac arrest have been associated with propofol. 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: (See WARNINGS and DOSAGE AND ADMINISTRATION, Handling Procedures.) The administration of propofol 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 CLINICAL PHARMACOLOGY - Individualization of Dosage.)

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 propofol, I.V. fluid administration, and/or vasopressor therapy.

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

Failure to reduce the infusion rate in patients receiving propofol 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 propofol infusion for ICU sedation, especially of long duration.

Opioids and paralytic agents should be discontinued and respiratory function optimized prior to weaning patients from mechanical ventilation. Infusions of propofol 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 propofol, abrupt discontinuation of a patient's infusion may result in rapid awakening of the patient with associated anxiety, agitation, and resistance to mechanical ventilation, making weaning from mechanical ventilation difficult. It is, therefore, recommended that administration of propofol be continued in order to maintain a light level of sedation throughout the weaning process until 10-15 minutes prior to extubation at which time the infusion can be discontinued.

Since propofol injectable emulsion is formulated in an oil-in-water emulsion, elevations in serum triglycerides may occur when propofol 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 propofol 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 propofol injectable emulsion formulation; 1 mL of propofol injectable emulsion contains approximately 0.1 g of fat (1.1 kcal).

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non asthmatic people.

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

Neurosurgical Anesthesia: When propofol 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 propofol. 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 propofol. (See DOSAGE AND ADMINISTRATION.)

Cardiac Anesthesia: Slower rates of administration should be utilized in premedicated patients, geriatric patients, patients with recent fluid shifts, or patients who are hemodynamically unstable. Any fluid deficits should be corrected prior to administration of propofol. 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 propofol.

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 propofol 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 propofol 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 propofol 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 propofol has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of propofol.

Propofol 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.

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: Teratogenic Effects, 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: Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta; and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression.

Nursing Mothers: Propofol is not recommended for use in nursing mothers because propofol 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: Propofol is not recommended for use in pediatric patients for ICU or MAC sedation. In addition, propofol is not recommended for general anesthesia for children below the age of 3 years because safety and effectiveness have not been established.

Although no causal relationship has been established, serious adverse events (including fatalities) have been reported in children given propofol for ICU sedation. These events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

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 propofol 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 propofol 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 propofol during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea.

Anesthesia in Children

Generally the adverse experience profile from reports of 349 propofol pediatric patients between the ages of 3 and 12 years in the US/Canadian anesthesia clinical trials is similar to the profile established with propofol 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) 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

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: Teratogenic Effects, 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: Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta; and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression.

Nursing Mothers: Propofol is not recommended for use in nursing mothers because propofol has been reported to be excreted in human milk, and the effects of oral absorption of small amounts of propofol are not known.

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The following estimates of adverse events include data from clinical trials in ICU sedation (N=159) 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 Hypotension* [Peds: 17%] [Hypertension Peds: 8%] (see also CLINICAL PHARMACOLOGY)	Bradycardia, Decreased Cardiac Output, 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%]	

Events without an * or % had an incidence of 1%-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	
Cardiovascular:	Premature Atrial Contractions Syncope	
Central Nervous System:	Hypertonia/Dystonia, Paresthesia	Agitation
Digestive:	Hypersalivation	
Musculoskeletal:	Myalgia	
Respiratory:	Wheezing	Decreased Lung Function
Skin and Appendages:	Flushing, Pruritus	
Special Senses:	Amblyopia	
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, Hypernatremia	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 propofol by health care professionals have been reported, including some fatalities. Propofol 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, propofol 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

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors, including preinduction and concomitant medications, age, ASA physical classification, and level of debilitation of the patient.

The following is abbreviated dosage and administration information which is only intended as a general guide in the use of propofol. Prior to administering propofol, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY - Individualization of Dosage section.

In the elderly, debilitated, or ASA III/IV patients, rapid bolus doses should not be the method of administration. (See WARNINGS.)

Intensive Care Unit Sedation:

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS SODIUM METABISULFITE (0.25 MG/ML) TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL 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. (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES.)

Propofol should be individualized according to the patient's condition and response, blood lipid profile, and vital signs. (See PRECAUTIONS - ICU 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. Dosages of propofol should be reduced in patients who have received large dosages of narcotics. Conversely, the propofol 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 DOSAGE GUIDE.) **EVALUATION OF LEVEL OF SEDATION AND ASSESSMENT OF CNS FUNCTION SHOULD BE CARRIED OUT DAILY THROUGHOUT MAINTENANCE TO DETERMINE THE MINIMUM DOSE OF PROPOFOL REQUIRED FOR SEDATION. (SEE Clinical Trials, 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.)

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

SUMMARY OF DOSAGE GUIDELINES - Dosages and rates of administration in the following table should be individualized and titrated to clinical response. Safety and dosage requirements in pediatric patients have only been established for induction and maintenance of anesthesia. For complete dosage information, see CLINICAL PHARMACOLOGY - Individualization of Dosage.

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 III/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 - healthy, 3 years of age or older:** 2.5 to 3.5 mg/kg administered over 20-30 seconds.
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, or ASA III/IV Patients:** 50 to 100 mcg/kg/min (3 to 6 mg/kg/h). **Cardiac Anesthesia:** Most patients require: Primary Propofol with Secondary Opioid - 100-150 mcg/kg/min Low Dose Propofol with Primary Opioid - 50-100 mcg/kg/min (See CLINICAL PHARMACOLOGY Table 4.) **Neurosurgical Patients:** 100 to 200 mcg/kg/min (6 to 12 mg/kg/h). **Pediatric - healthy, 3 years of age or older:** 125 to 300 mcg/kg/min (7.5 to 18 mg/kg/h).
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 III/IV**

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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 III/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 lingering 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 level of sedation is achieved. Maintenance rates of 5 to 50 mcg/kg/min (0.3 to 3 mg/kg/h) or higher may be required. **Evaluation of level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of propofol required for sedation.** **The tubing and any unused portions of propofol injectable emulsion should be discarded after 12 hours because propofol injectable emulsion contains no preservatives and is capable of supporting growth of microorganisms. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)**

Compatibility and Stability: Propofol injectable emulsion should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: Propofol injectable emulsion is provided as a ready to use formulation. However, should dilution be necessary, should only be diluted with 5% dextrose injection; and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In ated 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 stic).

Administration with Other Fluids: Compatibility of propofol injectable emulsion with the co-administration of blood/serum/plasma has not been ablished. (See WARNINGS.) Propofol injectable emulsion has been shown to be compatible when administered with the following intravenous flu-

Dextrose Injection (5%)
Lactated Ringers and Dextrose (5%)
Dextrose (5%) and Sodium Chloride (0.45%) Injection
Dextrose (5%) and Sodium Chloride (0.2%) injection

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renteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and con- r permit.

ncial experience with the use of in-line filters and propofol injectable emulsion during anesthesia or ICU/MAC sedation is limited. Propofol injectable sion should only be administered through a filter with a pore size of 5 microns or greater unless it has been demonstrated that the filter does not ct the flow of propofol injectable emulsion and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically opriate. Continuous monitoring is necessary due to the potential for restricted flow and/or breakdown of the emulsion.

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

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Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

Propofol injectable emulsion should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The vial rubber stopper should be disinfected using 70% isopropyl alcohol. Propofol injectable emulsion should be drawn into sterile syringes immediately after vials are opened. When withdrawing propofol injectable emulsion from vials, a sterile vent spike should be used. Administration should commence promptly and be completed within 6 hours after the vials have been opened.

Propofol injectable emulsion should be prepared for single patient use only. Any unused portions of propofol injectable emulsion, reservoirs, dedicated administration tubing and/or solutions containing propofol injectable emulsion must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The I.V. line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual propofol injectable emulsion.

Guidelines for Aseptic Technique for ICU Sedation

Propofol injectable emulsion should be prepared for single patient use only. When propofol 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 propofol injectable emulsion. As with other lipid emulsions, the number of I.V. 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 propofol injectable emulsion must be discarded after 12 hours.

If propofol 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 6 hours.

HOW SUPPLIED

Propofol injectable emulsion is available in ready-to-use 20 mL vials, 50 mL infusion vials, and 100 mL infusion vials containing 10 mg/mL of propofol.

Vials:

NDC Number	Propofol	Available Packaging
0703-2856-04	20 mL vial	25 vials/shelf tray
0703-2856-09	50 mL infusion vial	20 vials/shelf tray
0703-2859-03	100 mL infusion vial	10 vials/shelf tray

Propofol undergoes oxidative degradation in the presence of oxygen, and is, therefore, packaged under nitrogen to eliminate this degradation path. Store between 4°-22°C (40°-72°F). Do not freeze. Shake well before use.

R_x only

Issued: December 1998
Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA 92618

GensiaSicor™ PHARMACEUTICALS

NDC 0703-**2859-03**

Propofol
Injectable Emulsion 1%

1000 mg/100 mL
(10 mg/mL)

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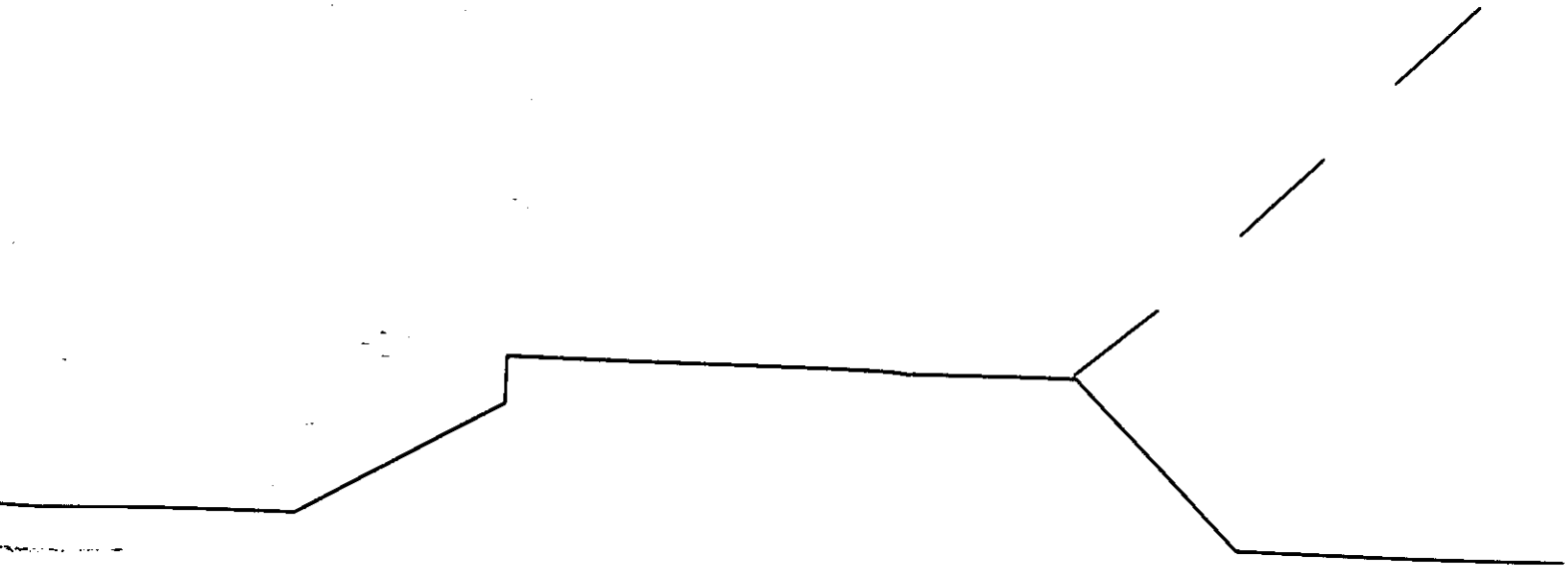
- Use strict aseptic tech..ique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE: microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

Sterile, nonpyrogenic

10 x 100 mL single-patient infusion vial

Contains a Sulfite



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GensiaSicor™ PHARMACEUTICALS

NDC 0703-2859-03

Propofol
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Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

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GensiaSicor™ PHARMACEUTICALS

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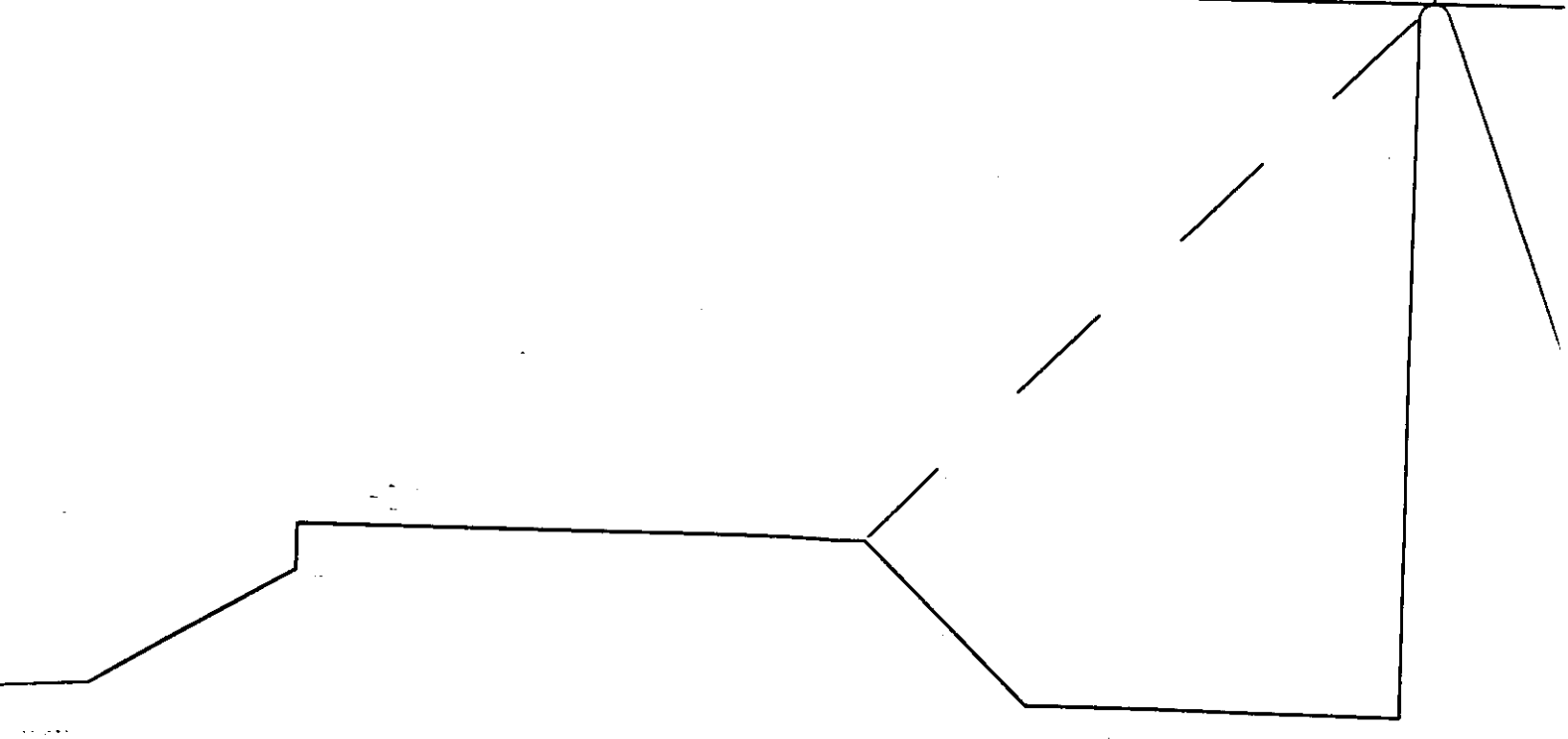
10 x 100 mL single-patient infusion vials

Contains a Sulfite



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- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

SHAKE WELL BEFORE USE.

Usual Dosage: See insert.

Each mL contains: propofol (10 mg), soybean oil (100 mg), glycerol (22.5 mg), egg yolk phospholipid (12 mg) and **SODIUM METABISULFITE** (0.25 mg); with sodium hydroxide to adjust pH to 4.5-6.4.

Propofol 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. **Patients should continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

Store between 4°-22°C (40°-72°F). Do not freeze. Discard unused portion.

Rx only

X12-285-901

GensiaSicor

NDC 0703-2856-04

Propofol

Injectable Emulsion 1%

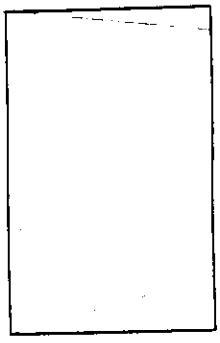
200 mg/20 mL

FOR I.V. ADMINISTRATION

Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- **CONTAINS A SULFITE:** microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

25 x 20 mL single dose vials
Contains a Sulfite



GensiaSicor

NDC 0703-2856-04

Propofol

Injectable Emulsion 1%

200 mg/20 mL

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- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE: microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

25 x 20 mL single dose vials
Contains a Sulfite

SHAKE WELL BEFORE USE.

Usual Dosage: See insert.

Each mL contains: propofol (10 mg), soybean oil (100 mg), glycerol (22.5 mg), egg yolk phospholipid (12 mg), and SODIUM METABISULFITE (0.25 mg), with sodium hydroxide to adjust pH to 4.5-6.4.

Propofol 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. 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.

Store between 4°-22°C (40°-72°F). Do not freeze. Discard unused portion.

R_x only

X12-285-601

APPROVED

FOR I.V. ADMINISTRATION

Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

25 x 20 mL single dose vials
Contains a Sulfite

2856-04
ɔfol
ıulsion 1%
0 mL
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ISTRATION
ıc., Irvine, CA 92618

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE; microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

25 x 20 mL single dose vials
Contains a Sulfite

GensiaSicor

NDC 0703-**2856-04**
Propofol
Injectable Emulsion 1%
200 mg/20 mL

FOR I.V. ADMINISTRATION
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

APPROVED

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE; microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

25 x 20 mL single dose vials
Contains a Sulfite

GensiaSicor

NDC 0703-**2856-04**
Propofol
Injectable Emulsion 1%
200 mg/20 mL

FOR I.V. ADMINISTRATION
Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618

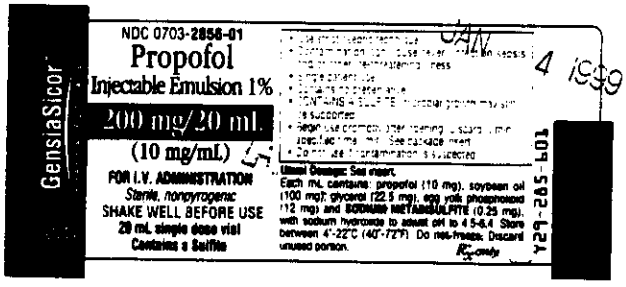
- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE; microbial growth may still be supported.
- Begin use promptly after ope
(See package insert.)
- Do not use if contamination

25 x 20 mL single
Contains a Sulfite

Container Label - NDC 0703-2856-04

(Part No. Y29-285-601)

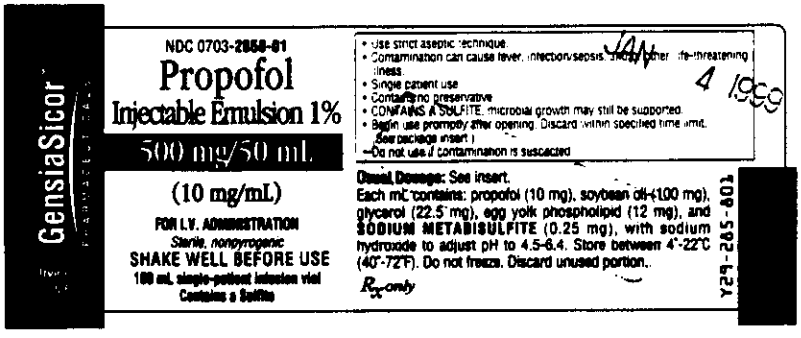
200 mg/20 mL vial



Container Label - NDC 0703-2858-09

(Part No. Y29-285-801)

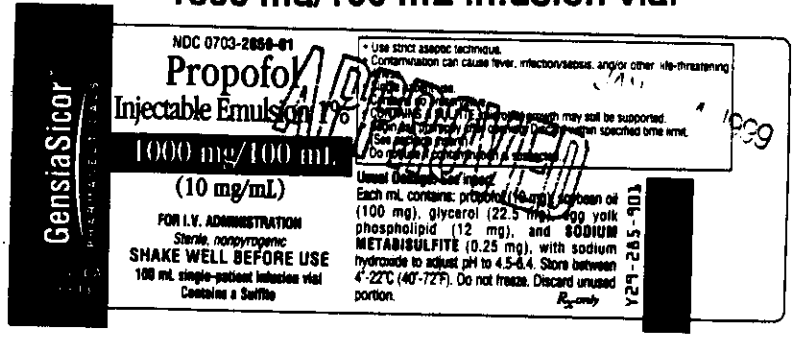
500 mg/50 mL infusion vial



Container Label - NDC 0703-2859-03

(Part No. Y29-285-901)

1000 mg/100 mL infusion vial



GensiaSicor™ PHARMACEUTICALS

NDC 0703-**2858-09**

Propofol

Injectable Emulsion 1%

500 mg/50 mL

(10 mg/mL)

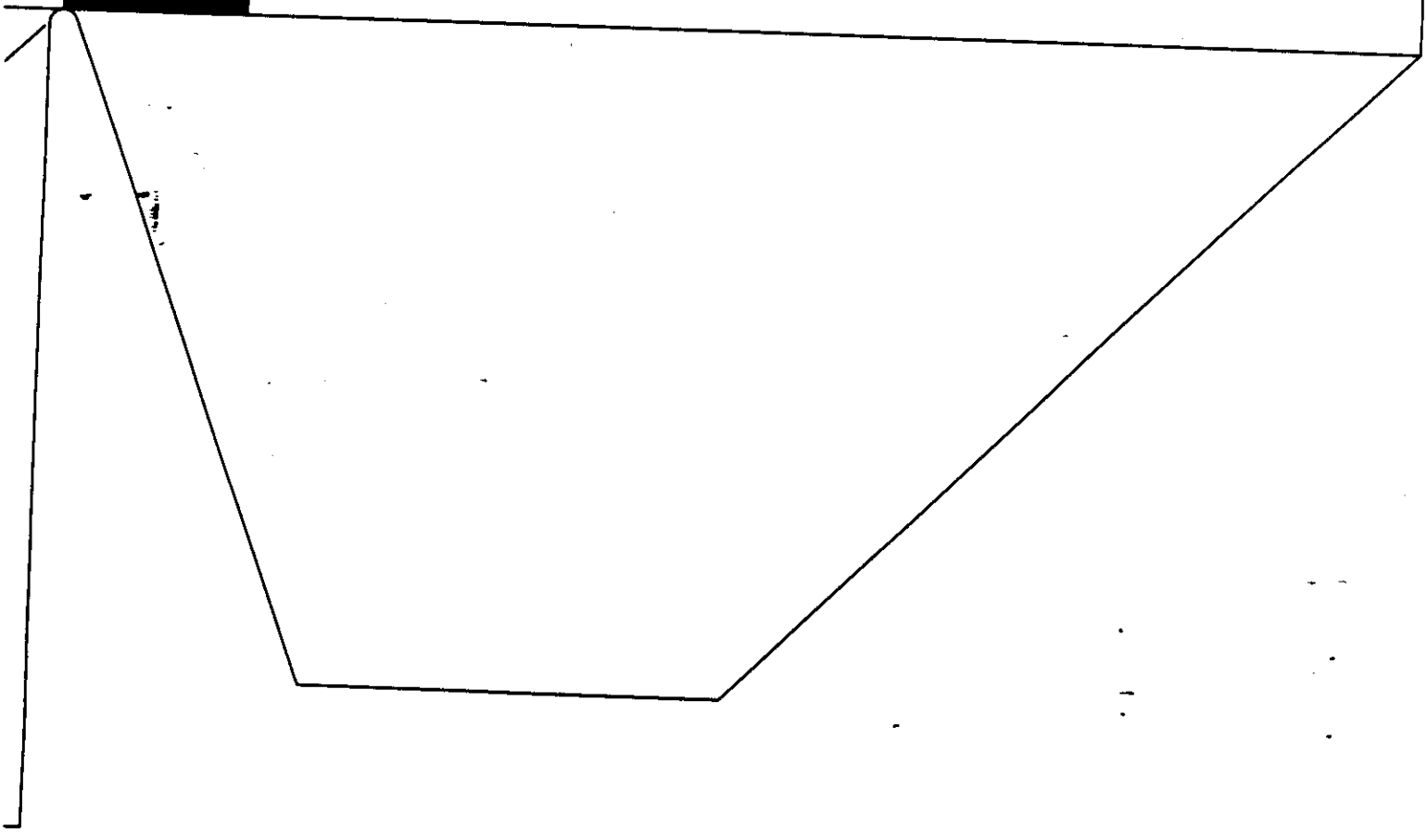
FOR I.V. ADMINISTRATION

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE; microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

Sterile, nonpyrogenic

20 x 50 mL single-patient infusion vials

Contains a Sulfite



NDC 0703-**2858-09**

JAN 4 1999

APPROVED

Propofol

Injectable Emulsion 1%

500 mg/50 mL

(10 mg/mL)

FOR I.V. ADMINISTRATION

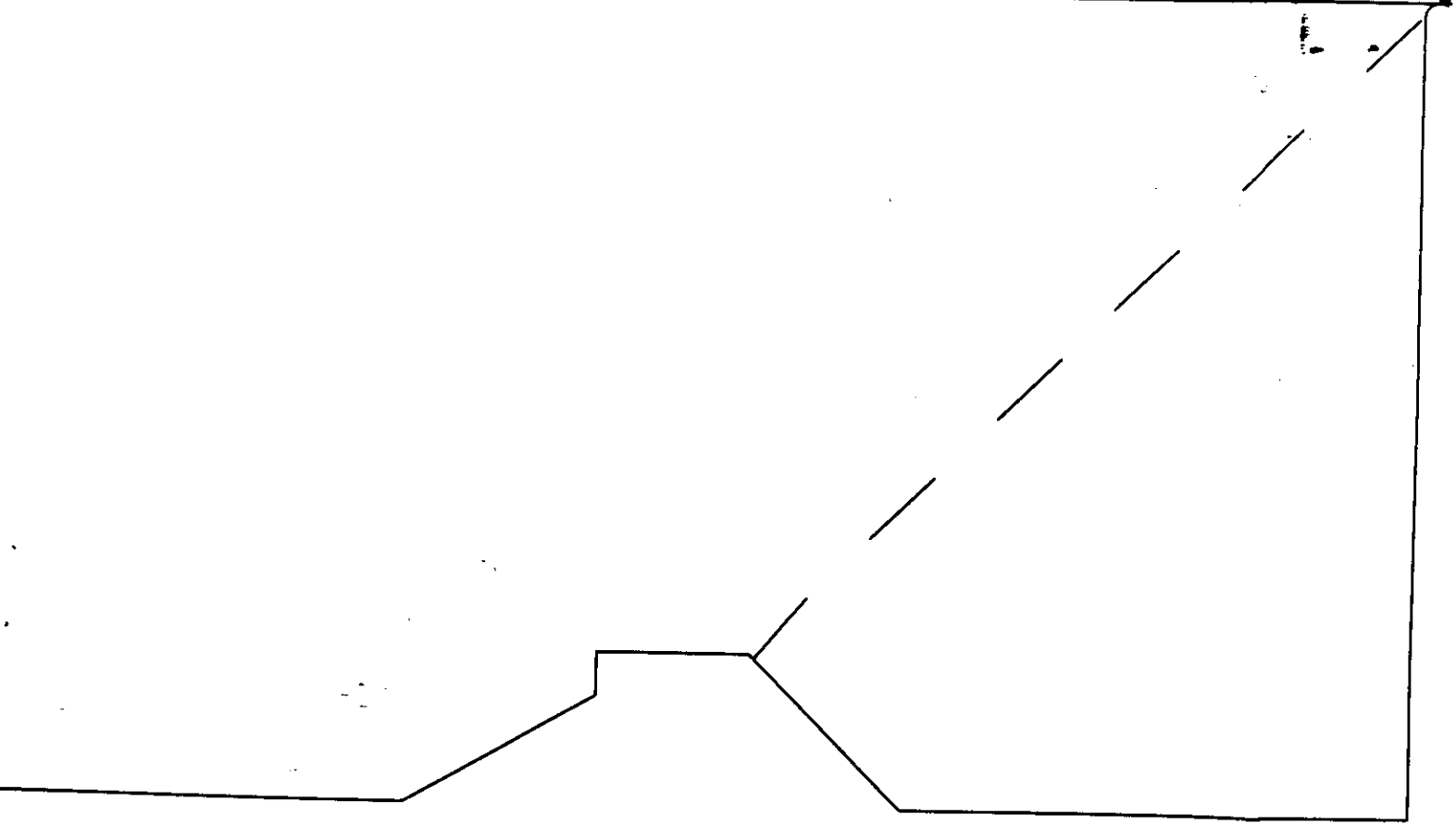
GensiaSicor Pharmaceuticals, Inc., Irvine, CA 92618

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE: microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

Sterile, nonpyrogenic

20 x 50 mL single-patient infusion vials

Contains a Sulfite



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GensiaSicor™ PHARMACEUTICALS

NDC 0703-**2858-09**

Propofol

Injectable Emulsion 1%

500 mg/50 mL

(10 mg/mL)

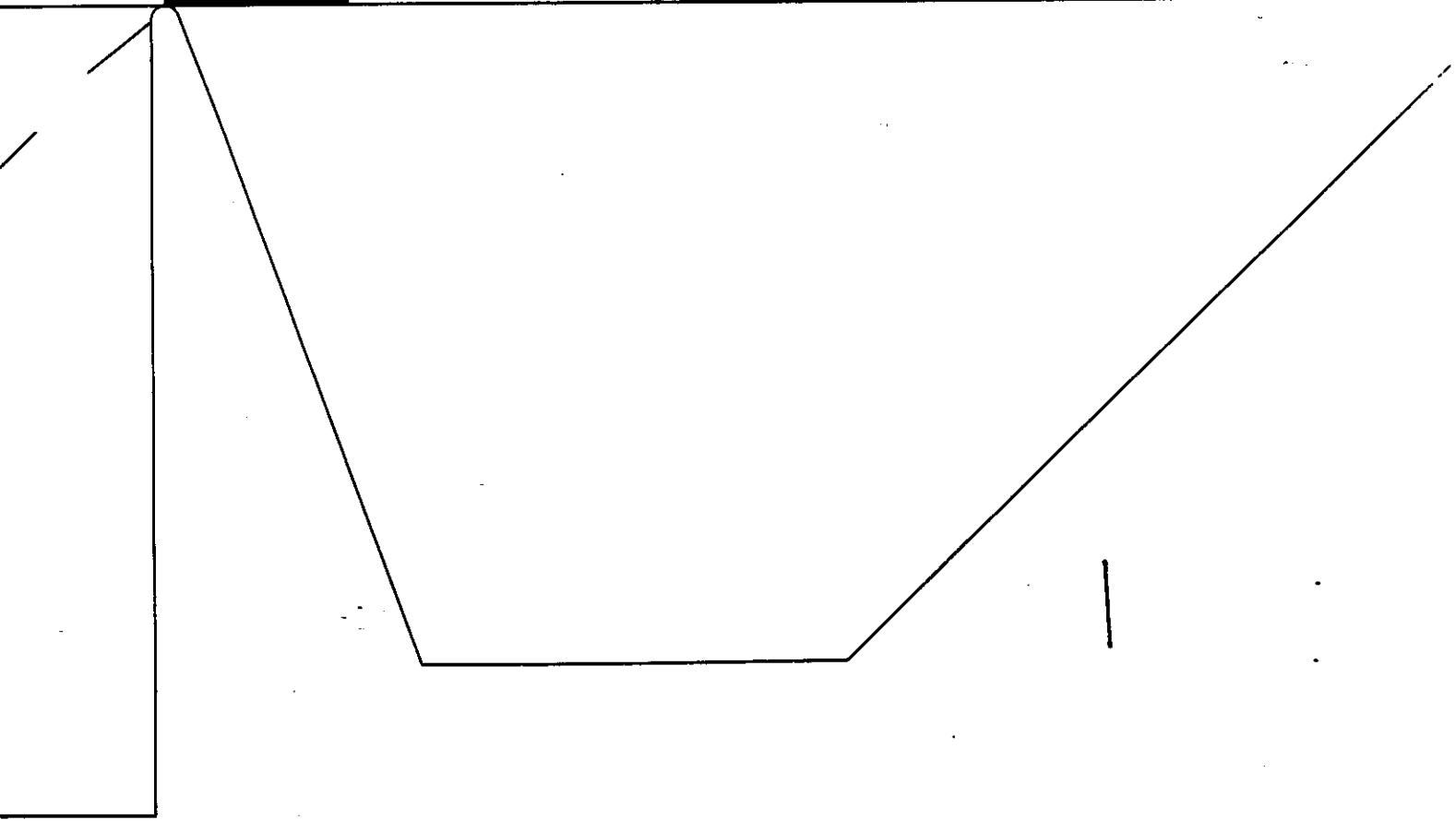
FOR I.V. ADMINISTRATION

- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE: microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

Sterile, nonpyrogenic

20 x 50 mL single-patient infusion vials

Contains a Sulfite



- Use strict aseptic technique.
- Contamination can cause fever, infection/sepsis, and/or other life-threatening illness.
- Single patient use.
- Contains no preservative.
- CONTAINS A SULFITE; microbial growth may still be supported.
- Begin use promptly after opening. Discard within specified time limit. (See package insert.)
- Do not use if contamination is suspected.

SHAKE WELL BEFORE USE.

Usual Dosage: See insert.

Each mL contains: propofol (10 mg), soybean oil (100 mg), glycerol (22.5 mg), egg yolk phospholipid (12 mg) and **SODIUM METABISULFITE** (0.25 mg); with sodium hydroxide to adjust pH to 4.5-6.4.

Propofol 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. **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.**

Store between 4°-22°C (40°-72°F). Do not freeze. Discard unused portion.

Rx only

Gensia Sicor Pharmaceuticals, Inc., Irvine, CA 92618 X12-285-801

Gensia Sicor™

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA #75-102

3. NAME AND ADDRESS OF APPLICANT
Gensia Sicor Pharmaceuticals
17 Hughes
Irvine, CA 92718-1902

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Zeneca, Ltd., Diprivan® (NDA 19-627).
Patent certification and exclusivity statement are provided (pp 013-017).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Propofol Injectable Emulsion (With 0.025% Sodium Metabisulfite)

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		FDA	
Orig. submission	3/31/97	Acknowledgment letter	5/8/97
Amendment	5/20/97		
		Micro review	9/17/97
		Deficiency letter	10/22/97
Amendment (Bio)	12/11/97		
Amendment	12/3/97		

Change to 0.025% Sodium Metabisulfite

Amendment	1/16/98		
New correspondence	2/11/98		
New correspondence	4/13/98		
New correspondence	5/27/98	Bio review (Final)	6/23/98
New correspondence	6/30/98		
New correspondence	8/10/98		
Amendment	8/24/98	Micro review	10/23/98
Amendment	10/16/98		
Amendment	12/14/98		
New correspondence	12/15/98	Label review	12/21/98
New correspondence	12/28/98		

10. PHARMACOLOGICAL CATEGORY
Anesthetic - is indicated for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

11. Rx or OTC
Rx

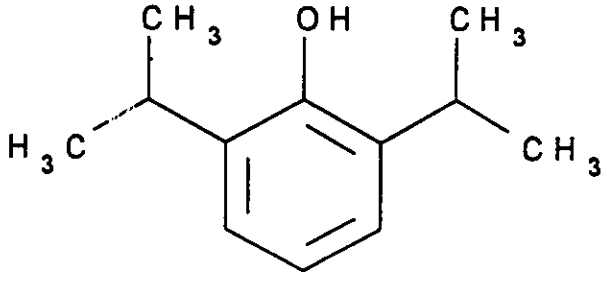
12. RELATED ANDA/DMF(s)

13. DOSAGE FORM
Injection (I.V. Administration)

14. STRENGTH
10 mg/ml

15. CHEMICAL NAME AND STRUCTURE

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



2,6-Diisopropylphenol. CAS [2078-54-8]

Drug substance and drug product are not official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS

a. Application is **satisfactory** for approval
b. Labeling review **ACCEPTABLE**, dated 12/21/98
c. Bio review found **ADEQUATE**, dated 6/23/98
d. Micro review found **ADEQUATE**, dated 10/23/98
d. DMF found **ADEQUATE**, dated 11/17/98
e. Methods validation for drug substance and drug product have been evaluated under ANDA 74-816. Only the sodium metabisulfite assay was tested on this ANDA.
f. Establishment Evaluation Report has been found **ADEQUATE**, dated 12/14/98.
g. ANDA has same manufacturing process as companion ANDA 74-816 (vials).

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER — Raymond Brown

DATE COMPLETED — December 28, 1998

Page(s) 13

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2

12/28/98

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/22/97

Chemistry Comments

#35

1. CHEMIST'S REVIEW NO.1

2. ANDA #75-102

3. NAME AND ADDRESS OF APPLICANT
Gensia Laboratories, Ltd.
19 Hughes
Irvine, CA 92718-1902

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Zeneca, Ltd., Diprivan® (NDA 19-627). Patent certification and exclusivity statement are provided (pp. 013-017).

U.S. Patent No. 4056635, expired November 1, 1996

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Propofol Injectable Emulsion 1% (Wit

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		FDA	
Orig. submission	3/31/97	Acknowledgment letter	5/8/97
		CSO review	4/29/97
		Label review	Pending
Amendment	5/20/97	Bio review	Pending
		Micro review	9/17/97

This review covers submissions dated 3/31/97 and 5/20/97.

10. PHARMACOLOGICAL CATEGORY
Anesthetic - is indicated for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

11. Rx or OTC
℞

12.

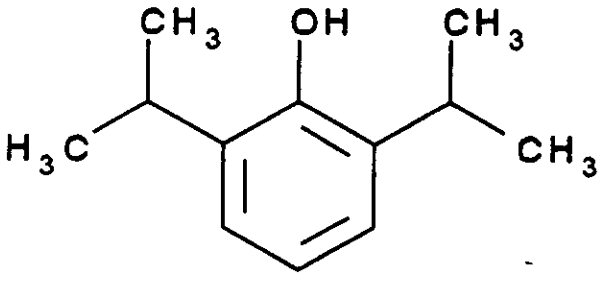
13. DOSAGE FORM
Injection (I.V. Administration)

14. STRENGTH
10 mg/ml

15. CHEMICAL NAME AND STRUCTURE

Propofol

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



2,6-Diisopropylphenol. CAS [2078-54-8]

Drug substance and drug product are not official USP 23 items.

16. RECORDS AND REPORTS None

17. COMMENTS
    a. Application contains **facsimile** CMC deficiencies
    b. Labeling **pending** dated.
    c. Bio (with found **pending**, dated
    d. Micro found **satisfactory**, dated 9/17/97
    d. DMF found **satisfactory**, dated 7/25/97
    e. Methods validation for both drug substance and drug is being evaluated under ANDA 74-816, submitted 4/7/97.
    f. Establishment Evaluation Request has been submitted to the Division of Compliance, dated 4/30/97.
    g. ANDA has same manufacturing process as companion ANDA 74-816 (vials).

18. CONCLUSIONS AND RECOMMENDATIONS

NOT APPROVABLE

19. REVIEWER: Raymond Brown

DATE COMPLETED: July 25, 1997

Page(s) 15

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #1

7/25/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

BIOEQUIVALENCE REVIEW(S)

7.1

Propofol Injectable Emulsion
10 mg/mL
ANDA #75-102
Review: Moheb H. Makary
Filename: 75102W.198

Gensia Laboratories
Irvine, CA
Submission Date:
1/16/1998

Addendum to the January 16, 1998 Review

Gensia's formulation for Propofol Injectable Emulsion, 10 mg/mL, contains 0.025% sodium metabisulfite instead of used in the reference product by Zeneca. Therefore, the waiver for the test product should be granted based on CFR 320.24(b)(6) not on CFR 320.22 (b)(1) as stated in the original review (review dated June 23, 1998).

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

Concur /S/ Date: 12/30/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Propofol Injectable Emulsion
10 mg/mL
ANDA #75-102
Review: Moheb H. Makary
Filename: 75102W.198

Gensia Laboratories
Irvine, CA
Submission Date:
1/16/1998

Addendum to the January 16, 1998 Review

Gensia's formulation for Propofol Injectable Emulsion, 10 mg/mL, contains 0.025% sodium metabisulfite instead of used in the reference product by Zeneca. Therefore, the waiver for the test product should be granted based on CFR 320.24(b)(6) not on CFR 320.22 (b)(1) as stated in the original review (review dated June 23, 1998).

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

/S/

Concur: _____ Date: 12/30/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/12-30-98, 75102W.D98

DIVISION REVIEW SUMMARY

ANDA 75-102 **DRUG PRODUCT:** Propofol Injection Emulsion (with 0.025% Sodium Metabisulfite)

FIRM: Gensia Sicor Pharmaceuticals

DOSAGE FORM: Injectable (Intravenous)

STRENGTH(S): 10 mg/mL

cGMP STATEMENT/EIR UPDATE STATUS: Adequate -
An **ESTABLISHMENT EVALUATION REPORT** issued to the Division of Compliance has found to be ADEQUATE, dated 12/14/98.

BIO INFORMATION: Satisfactory -
The Division of Bioequivalence has granted the waiver is pending the acceptance of the new formulation. See bio review dated 6/23/98.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Adequate -

Methods validation for drug substance and drug product were performed under ANDA 74-816, which used the same methods. Only the sodium metabisulfite assay was tested on ANDA 75-102. See methods validation report dated May 26, 1998.

STABILITY: Satisfactory -
Accelerated (40°C ± 2°C/75 ± 5% RH and Light Box) stability data are provided for lot nos. XP7N314, XP7S302 and XP7S302F1 tested at 1, 2 and 3 month intervals in the final marketed container/closure systems, 20 mL, 50 mL and 100 mL vials respectively. The data are adequate and within the specified limits. Also provided are controlled room temperature (22 ± 2°C and 25 ± 2°C/60 ± 5% RH), tested at 1, 2, 3, 6 and 9 month intervals in the final container/closure systems. The data are within the specified limits. An expiration dating period of 24 month has been granted.

LABELING: Acceptable -
See review of professional labeling conducted by Kuong Lee, concurred by John Grace, dated 12/16/98.

STERILIZATION VALIDATION: Adequate -
See micro review #2, dated 10/23/98.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Batch nos. XP7N314 NDS lot no. PL-PROP-4) has a theoretical yield of Liters, actual yield consist of Liters.

Drug Master File found **ADEQUATE**, dated 11/17/98.

SIZE OF STABILITY BATCHES - Satisfactory -
Batch no. XP7N314 a theoretical yield of Liters, actual yield consist of .iters. Batch Reconciliation indicates the entire batch was packaged in to sublots, lot no. XP7S302 and XP7S302F1.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Satisfactory -

The proposed maximum production batch size is iters, with equipment specified.

RECOMMENDATION:

APPROVE

cc:

Endorsement: 12/28/98

-/95

GENSIA
LABORATORIES, LTD.

December 11, 1997

NDA ORIG AMENDMENT

n/a s

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion (with 0.005% EDTA), 10 mg/mL Prefilled Syringe ANDA: 75-102

BIOEQUIVALENCY AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Propofol Injectable Emulsion (Prefilled Syringe) containing 0.005% Disodium Edetate (EDTA) in the formulation, ANDA 75-102. Reference is also made to the Agency's letter dated November 30, 1997. In accordance with the provisions of Section 314.96 of the Code of Federal Regulations, Title 21, we hereby amend our application to provide the additional information as requested.

Furthermore, pursuant to the Agency's instructions, a copy of the Bioequivalency Deficiency facsimile is provided in this response.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting Ms. Rosalie A. Lowe, Associate Director, Regulatory Affairs, at (714) 457-2808, or myself at (714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

RECEIVED
DEC 12 1997
GENERIC DRUGS

Enclosure
cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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NOV 30 1997

J. Behrens

4

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-102 APPLICANT:GENSIA

DRUG PRODUCT: Propofol 10 mg/ml prefilled syringes (injectable emulsion)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

1. Please measure the globule size distribution in the prefilled syringes for both the test and reference products.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-102 APPLICANT:GENSIA

DRUG PRODUCT: Propofol 10 mg/ml prefilled syringes (injectable emulsion)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

1. Please measure the globule size distribution in the prefilled syringes for both the test and reference products.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Propofol Injection, Prefilled Syringe	Gensia Laboratories
10 mg/mL	Irvine, CA
ANDA #75-102	Submission Date:
Reviewer: Moo Park	3/31/97; 5/20/97
Filename: 75102w.397	

Review of a Waiver Request

I. Objectives

Review of Gensia's waiver request for its Propofol Injection, 10 mg/mL in 20 mL prefilled syringe. Reference listed drug product is Zeneca's Diprivan®, 10 mg/mL in 50 mL prefilled syringe.

II. Background

The applicant received a waiver for its Propofol Injection, 10 mg/mL in 20 mL, 50 mL and 100 mL vials (ANDA #74-816; submission date=12/24/96; review date=5/16/97). This ANDA #75-102 is for Propofol Injection, 10 mg/mL in 20 mL prefilled syringe.

III. Comments

1. Propofol Injection is an oil-in-water emulsion. The formulation of the test product is shown below. The formulations of the test and reference formulations are identical.

Test Formulation

Ingredient	Amount mg/mL
Propofol	10
Soybean Oil, USP	100
Glycerin, USP	22.5
Egg Lecithin	12
Sodium Hydroxide	qs to pH 7-8.5
Water for Injection, USP	qs to 1 mL

2. The globule size distribution data of the test and reference drug products submitted were the same submitted for ANDA #74-816 for the injectable emulsion packaged in vials. The firm should measure the globule size distribution in the prefilled syringe formulation for both the test and reference products. Variables such as filling operation into syringes and contact with packaging components may affect the globule size distribution.

3. The waiver of *in vivo* bioequivalence study requirements for the test product is not granted pending the applicant's new globule size distribution data for the test and reference products packaged in syringes.

IV. Deficiency

The globule size distribution data of the test and reference drug products submitted were the same submitted for ANDA #74-816 for the injectable emulsion packaged in vials. The firm should measure the globule size distribution in the prefilled syringes for both the test and reference products.

V. Recommendation

The Division of Bioequivalence does not agree that the information submitted by Gensia demonstrates that its Propofol Injection (with), 10 mg/mL in prefilled syringe, falls under 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The submission is incomplete and the waiver of *in vivo* bioequivalence study requirements for the test product is not granted pending the applicant's response to the deficiency.

The firm should be informed of the deficiency and recommendation.

/S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 7/9/97

Concur: /S/ Date: 8/1/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

File history: Draft (7/2/97); Final (7/8/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologists Review #1
September 15, 1997

A. 1. ANDA 75-102

APPLICANT Gensia Laboratories, LTD.
19 Hughes
Irvine CA 92718-1902

2. PRODUCT NAMES: **Propofol Injectable Emulsion (with 0.005% EDTA)**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10 mg/mL Emulsion, 200 mg/20 mL Pre-Filled Syringes, Intravenous

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Hypnotic Agent (Sedative)

B. 1. DATE OF INITIAL SUBMISSION: **March 31, 1997**
Subject of this Review **(Received April 1, 1997)**

2. DATE OF AMENDMENT: None
3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 9/8/97

C. REMARKS: The subject drug product is filled into 20 mL glass syringes and terminally sterilized at the Irvine CA pharmaceutical manufacturing facility.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. The specific comments are provided in "E. Review Notes".

/S/ 9/16/97
Andrea S. High, Ph. D.

cc:

9/17/97

Page(s) 4

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Micro Review #1

9/15/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

ADMINISTRATIVE DOCUMENTS

Verified 12/30/98 Quality

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: ANDA 75102/000
Stamp: 01-APR-1997 Regulatory Due:
Applicant: GENSIA LABS
19 HUGHES
IRVINE, CA 926181902

Priority:
Action Goal:
Brand Name:
Established Name: PROPOFOL
Generic Name:
Dosage Form: INJ (INJECTION)
Strength: 10MG/ML

Org Code: 600
District Goal: 01-JUN-1998

FDA Contacts: K. SHERROD (HFD-617) 301-827-5849 , Project Manager
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 14-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 12-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 16-NOV-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 2027158
GENSIA INC
19 HUGHES
IRVINE, CA 926181902

DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-102** Date of Submission: **December 14, 1998**

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Approval Summary

Do you have 12 Final Printed Labels and Labeling? YES

1. CONTAINER - 20 mL, 50 mL, and 100 mL vials

   Satisfactory in FPL in the December 14, 1998 submission.

2. CARTON - 20 mL, 50 mL, and 100 mL

   Satisfactory in FPL in the December 14, 1998 submission.

3. INSERT

   Satisfactory in FPL in the December 14, 1998 submission.

Revisions Needed Post Approval But Prior To Marketing

1. CONTAINER - 20 mL, 50 mL, and 100 mL vials

   a. Please add "Contains a Sulfite" with the **same prominence** as the total volume expression on the principal display panel and relocate to appear above the route of administration.

   b. Relocate "Rx only" to appear on the principal display panel.

2. CARTON - 20 mL, 50 mL, and 100 mL

   a. Relocate "Contains a Sulfite" to appear above the route of administration on the principal display panel.

   b. Relocate "Rx only" to appear on the principal display panel.

see Commitment by firm dated 12/21/98 on DFS to be made as SSCBE.

3. Transfer Label

Transfer labels are not reviewed by the Division however, we recommend that the phrase "Contains a Sulfite" be added to the label.

4. INSERT

a. The molecular weight of propofol should be 178.27 instead of 178.28 and chemically it should be described as 2,6-diisopropylphenol in the DESCRIPTION section.

b. Insert the word "injection" after the word "propofol" in the last sentence under Individualization of Dosage subsection of CLINICAL PHARMACOLOGY section.

c. Insert the word "classified" between the words "... recommended for children" and "ASA III or IV." in the fourth sentence, first paragraph, under Induction of General Anesthesia subsection of Pediatric Anesthesia subsection of CLINICAL PHARMACOLOGY section.

d. We note that you have included the statement "Contains sodium metabisulfite, a sulfite that...in non asthmatic people" in the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections however, this statement should appear in WARNINGS section per 21 CFR 201.22(b).

e. Delete the last sentence, "Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction." in the fifth paragraph under PRECAUTIONS section.

f. Please add "The syringe(s) should be labeled with appropriate information including the date and time the vial was opened." as the fifth sentence in the first paragraph under the Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation subsection of the DOSAGE AND ADMINISTRATION section.

g. We encourage you to relocate "*R_x only*" to the TITLE section.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diprivan

NDA Number: 19-627

NDA DRUG Name:Diprivan

NDA Firm: Zeneca

Date of Approval of NDA Insert and supplement #: 6-11-96
Supplement - Formulation Revision (SCF-027) only in draft which could not be located by the last 3 labeling reviewers. The only labeling that could be obtained from the New Drug Division (ND) was the one Mr. David Kognistein personally found himself from the ND document room. The labeling, dated December 4, 1996, is not approved however, it is the only model labeling available and was used by previous labeling reviewers. Several requests have been made to get the approved RLD labels and labeling however we have not received any updated labeling nor seen any approved labeling supplements recently.

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? NO

Basis of Approval for the container labels: REGULATIONS

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the FF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, *Warning Statements that might be in red for the NDA*)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD

1. Gensia Laboratories originally submitted ANDA 75-102 for propofol injectable emulsion with 10 mg/mL prefilled syringe on March 31, 1997, as a result of several communications with OGD. The firm withdrew from this application the prefilled syringe with the nd amended the application to provide for an alternate preservative system, 0.025% Sodium Metabisulfite, in vial sizes, 20 mL, 50 mL, and 100 mL.

2. MODEL LABELING - NDA 19-627 Diprivan® Injectable Emulsion 1%; Zeneca LTD: Approved 4-21-95 labeling issues, and 6-11-96 Supplement - Formulation Revision (SCF-027) approved labeling, revised 5-96.

3. This is a potential first generic.

4. INACTIVE INGREDIENTS - See page 100095 Section VIII, Volume 3.1. Note RLD cites Gensia cites "Glycerol" on the labels and labeling but Glycerin in the Components/Composition section. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable. It should be noted that the pH is now listed as 4.5 - 6.4 compared to 7 to 8.5. The pH difference was found to be acceptable by Dr. Mary Fanning.

5. PATENTS/EXCLUSIVITIES

Confirmed through Orange Book Cumulative Supplement 6 Jan'98-Jun'98.

Patent 4056635 expired 11-1-96.

Patent 4798846 expires on 3-19-97.

Patent 5714520 expires on March 22, 2015. Gensia states that this patent "will not be infringed upon by the manufacture, use, or sale by Gensia Sicor Pharmaceuticals, Inc., for which this amendment is submitted." Paragraph IV Certification cited.

Patent 5731355 provides for method of producing analgesia **expires March 22, 2015. Paragraph IV Certification cited.**

Patent 5731356 provides for a method for limiting the potential for microbial growth **expires March 22, 2015. Paragraph IV Certification cited.**

Exclusivities, I-99, for Pediatric Anesthesia in Children 3 years and older expired on 10-26-96.

Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96.

Exclusivity, NP, for new product containing expires on **June 11, 1999.** According to the information listed in the 18TH edition of the Approved Drug Products, Zeneca Ltd., has been granted a period of marketing exclusivity for Diprivan®. The exclusivity granted will expire on June 11, 1999. Indication: New Product. Gensia states that they are "not seeking marketing approval for an reserved (Propofol) Injectable Emulsion, 10 mg/mL product."

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
Not USP. Both ANDA and RLD: Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended.

The RLD storage recommendation has been revised to read "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

7. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission.

8. BIOEQUIVALENCE - Completed

9. PACKAGING CONFIGURATION
RLD: 20 mL ampuls, 50 mL and 100 mL infusion vials, and 20 mL and 50 mL pre-filled syringes.

ANDA: 20 mL single dose vials, and 50 mL and 100 mL infusion vials.

Earlier RLD labeling stated "Protect from light." However, newer labels do not have this statement. Also, in a previous review for another ANDA, the comment was made in the FTR that if packaged with nitrogen, the statement was not required.

10. The RLD has one revision in the box of warnings - "Supports rapid microbial growth" has been revised to read "Supports microbial growth". "Rapid" has been deleted. This does make sense based on the addition of retard growth. It is noted that this is not an antimicrobially preserved product under USP standards. To date, we have not received FPL for the 6-11/96 approved in draft for SCF labeling.

11. Gensia submitted an "IV Transfer Label". I have never seen such an approved label for the RLD. No comments will be made. We won't approve this. *This statement is from the previous review.*

12. BAIL BAND - A bail band will be attached to the bottom of each infusion vial.

13. TO FILTER OR NOT TO FILTER?

    See FTR dated 28-Apr-1997, from Laurence Landow, re: Innovator was told to delete the statement "Do not use in-line filters with this product". It was also noted on a memo dated 28-Feb-1997 that the Division was to send a letter to the innovator to delete the reference to the use of filters in the insert. Labels and labeling will be consistent to advise against the use of filters.

Date of Review: December 16, 1998 Dates of Submission: December 14, 1998

/S/

Primary Reviewer: Koung Lee

Team Leader: Charles V. Hoppes /S/ 12/21/98

cc:

Concur.
12/21/98

RECORD OF TELEPHONE CONVERSATION

I contacted Tania Hoffman today as a follow-up to her conversation with Charlie Heppes on 10/23/97.

She had questions regarding the review which was recently faxed to the firm.

After checking the jacket for ANDA 75-102, I was able to verify that the revision requested under CLINICAL PHARMACOLOGY: (Clinical Trials) ICU Sedation: (See WARNINGS...) Paragraph 6 - Revise the first sentence to read as follows: "In Medical Postsurgical ICU...". I confirmed that the "M" in Medical, and the "P" in Postsurgical must be capitalized.

I also confirmed the paragraph location for these corrections as paragraph 6.

DATE
10/24/97

ANDA NUMBER
75-102
74-816

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X
X FDA

MADE BY TELE. X
_ IN PERSON

PRODUCT NAME
Propofol Injectable Emulsion

FIRM NAME
Gensia Laboratories Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Tania Hoffman

TELEPHONE NUMBER
(714) 457-2848

SIGNATURE

X:\NEW\FIRMSAM\GENSIA\TELECONS\75102OCT.97

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-102** Dates of Submission: March 31, 1997

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

1. CONTAINER - 20 mL Single Dose Syringe

   a. Please ensure the statement "SHAKE WELL BEFORE USE" appears prominently.

   b. Revise the statement "In addition to... adjust pH" to read:

      "Each mL contains...".

   c. Revise the storage recommendation statement to read:

      ... (40°-72°F). Do Not Freeze. Discard ...

   d. Per the USP monograph titles, use "Edetate Disodium" rather than "Disodium Edetate" and "Edetate Calcium Disodium" rather than "Calcium Disodium Edetate."

2. CARTON - 20 mL Single Dose Syringe

   See comments under CONTAINER.

3. INSERT

   a. GENERAL COMMENTS

      i. We note that your ANDAs 75-102 and 74-816 share a common insert. Please note that if your applications are not approved at the same time you may be asked to change your insert labeling accordingly. Also, the following comments refer to the insert submitted on June 27, 1997, for ANDA 74-816.

      ii. Throughout the text of the insert do not

capitalize "propofol" unless required to do so by sentence structure.

b. CLINICAL PHARMACOLOGY:

Clinical Trials

ICU Sedation: (See WARNINGS...)
Paragraph 2 - Revise the first sentence to read as follows:

"In Medical Postsurgical ICU..."

c. PRECAUTIONS

i. **Intensive Care Unit Sedation: (See WARNINGS...)**

Paragraph 8, line 1 - "Edetate Calcium Disodium" rather than "Calcium Edetate Disodium".

ii. Paragraph 5 - Revise the last sentence as follows:

...days following induction. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial...

d. DOSAGE AND ADMINISTRATION (Administration with Other Fluids:)

i. Fifth paragraph, line 10 - **SEDATION (SEE CLINICAL PHARMACOLOGY, Clinical Trials...**

ii. Please revise the following strength of the Large Volume Parenterals to appear as follows:

Dextrose Injection 5%
Lactated Ringers and Dextrose (5%)
Dextrose (5%) and Sodium Chloride (0.45%) Injection
Dextrose (5%) and Sodium Chloride (0.2%) Injection

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling, and final print (or draft, if you prefer) insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

The project manager for these applications wanted us to make clear to the firm that the two applications can not be approved separately in this insert labeling since there is a shared insert.

I called Mr. Harrigan today to let him know this and to tell him that he can expect labeling comments soon for these applications.

DATE
10/21/97

ANDA NUMBER
74-816
75-102

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X
MADE BY TELE.

X FDA _
IN PERSON

PRODUCT NAME
Propofol Injectable Emulsion 1%

FIRM NAME
Gensia Laboratories, LTD

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Donald Harrigan

TELEPHONE NUMBER
(714)455-4700

SIGNATURE
/S/

E L E C T R O N I C M A I L M E S S A G E

Date: 22-Oct-1997 07:46am EDT
From: Mark Anderson
ANDERSONM
Dept: HFD-617 MPN2 E210
Tel No: 301-827-5848 FAX 301-443-3839

TO: Ramakant Mhatre (MHATRE)

CC:
CC:

Subject: Status of Bio Waiver for Gensia Propofol

Ram,

I see from bar code locator that you have (had?) the B1.1 volume and Moo's waiver review of 75-102 (Gensia Propofol in syringes). We have a chemistry package ready to FAX.

I there any reason to expect the waiver will be denied?

I see that we have granted a waiver to a sister application from Gensia for a vial application 74-816 (also reviewed by Moo).

Thanks,

Mark

CDER Establishment Evaluation Report
for October 09, 1997

Application: **ANDA 75102/000**
Stamp: **01-APR-1997** Regulatory Due:
Applicant: **GENSIA LABS**
19 HUGHES
IRVINE, CA 927181902

Priority:
Action Goal:
Brand Name:
Established Name: **PROPOFOL**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **10MG/ML**

Org Code: **600**
District Goal: **01-JUN-1998**

FDA Contacts: **K. SHERROD (HFD-617) 301-827-5849 , Project Manager**
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 12-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment: **2027158**
GENSIA INC
19 HUGHES
IRVINE, CA 927181902

DMF No:

AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 12-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Application: **ANDA 75102/000**
Stamp: **01-APR-1997** Regulatory Due:
Applicant: **GENSIA LABS**
19 HUGHES
IRVINE, CA 927181902

Priority:
Action Goal:
Brand Name:
Established Name: **PROPOFOL**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **10MG/ML**

Org Code: **600**
District Goal:

FDA Contacts: **K. SHERROD (HFD-617) 301-594-1300 , Project Manager**
B. ARNWINE (HFD-645) 301-594-1300 , Team Leader

Overall Recommendation:

Establishment

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment: **2027158**
GENSIA INC
19 HUGHES
IRVINE, CA 927181902

DMF No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-102** Dates of Submission: March 31, 1997

Applicant's Name: **Gensia Laboratories, Ltd.**

Established Name: **Propofol Injectable Emulsion 1% (10 mg/mL)**

Labeling Deficiencies:

1. CONTAINER - 20 mL Single Dose Syringe

   a. Please ensure the statement "SHAKE WELL BEFORE USE" appears prominently.

   b. Revise the statement "In addition to... adjust pH" to read:

      "Each mL contains...".

   c. Revise the storage recommendation statement to read:

      ... (40°-72°F). Do Not Freeze. Discard ...

   d. Per the USP monograph titles, use "Edetate Disodium" rather than "Disodium Edetate" and "Edetate Calcium Disodium" rather than "Calcium Disodium Edetate."

2. CARTON - 20 mL Single Dose Syringe

   See comments under CONTAINER.

3. INSERT

   a. GENERAL COMMENTS

      i. We note that your ANDAs 75-102 and 74-816 share a common insert. Please note that if your applications are not approved at the same time you may be asked to change your insert labeling accordingly. Also, the following comments refer to the insert submitted on June 27, 1997, for ANDA 74-816.

      ii. Throughout the text of the insert do not

capitalize "propofol" unless required to do so by sentence structure.

b. CLINICAL PHARMACOLOGY:

Clinical Trials

ICU Sedation: (See WARNINGS...)
Paragraph 2 - Revise the first sentence to read as follows:

"In Medical Postsurgical ICU..."

c. PRECAUTIONS

i. **Intensive Care Unit Sedation: (See WARNINGS...)**

Paragraph 8, line 1 - "Edetate Calcium Disodium" rather than "Calcium Edetate Disodium".

ii. Paragraph 5 - Revise the last sentence as follows:

...days following induction. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial...

d. DOSAGE AND ADMINISTRATION (Administration with Other Fluids:)

i. Fifth paragraph, line 10 - **SEDATION (SEE CLINICAL PHARMACOLOGY, Clinical Trials...**

ii. Please revise the following strength of the Large Volume Parenterals to appear as follows:

Dextrose Injection 5%
Lactated Ringers and Dextrose (5%)
Dextrose (5%) and Sodium Chloride (0.45%) Injection
Dextrose (5%) and Sodium Chloride (0.2%) Injection

Please revise your labels and labeling, as instructed above, and submit final printed container labels and carton labeling, and final print (or draft, if you prefer) insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		x	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, *Warning Statements that might be in red for the NDA*)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD: (portions brought forward from last review.)

1. MAJOR ISSUES - Gensia originally filed this ANDA with a non containing formulation. They received an NA letter dated 8-8-96 based on the original submission. They amended on 9-18-96. However, subsequently, they reformulated to add and amended again on 12-24-96. With this amendment, they withdrew the non- formulation for consideration. Thus, this review is of the container labels and carton and insert labeling of the new containing product.

2. MODEL LABELING - Diprivan® Injectable Emulsion 1%; Zeneca LTD: Approved 4-21-95 labeling issues, and 6-11-96 Supplement - Formulation Revision (SCF) approved labeling, revised 5-96.

3. This is a potential first generic.

4. INACTIVE INGREDIENTS - See page 100105 Section VII Volume 4.1. Note RLD cites "glycerin". Gensia cites "Glycerol" on labels, labeling. Glycerin USP monograph lists glycerol as an alternate name and this is acceptable. Also, Gensia chooses to refer to "Egg Lecithin" as "Egg yolk phospholipid". The chemist was consulted and finds this acceptable.

5. PATENTS/EXCLUSIVITIES - Confirmed through O Book Cumulative Supplement 6 Jan'97-Jun'97.
   Two patents: Patent 4056635 expired 11-1-96. Patent 4798846 expires on 3-19-97.
   Both exclusivities are now expired: I-99, for Pediatric Anesthesia in Children 3 years and older on 10-26-96. Exclusivity, I-90, for Intensive Care Unit Sedation expired on 3-8-96. Gensia certified incorrectly that both patents expired 11-1-96.

According to the information listed in the 17th edition of the Approved Drug Products, Zeneca Ltd., has been granted a period of marketing exclusivity for Diprivan®. The exclusivity granted will expire on June 11, 1999. Indication: New Product. Gensia does not intend to market this product prior to the expiration date of June 11, 1999.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
Not USP. Both ANDA and RLD: Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended.
The RLD storage recommendation has been revised to read "Store between 4° - 22°C (40° - 72°F). DO NOT FREEZE."

7. Gensia is the sole manufacturer of the drug product. See pp 335, 354 of original submission. ANDA has same manufacturing process as companion ANDA ~~75-102~~ 74-816 (vials).

8. BIOEQUIVALENCE - Pending. New waiver requested. See section VI of volume 4.1.

8. PACKAGING CONFIGURATION
RLD: 20 mL ampuls, 50 mL and 100 mL infusion vials, and 20 mL and 50 mL pre-filled syringes.

ANDA: 20 mL single dose vials, and 50 mL and 100 mL infusion vials, and 20 mL pre-filled syringes.

Earlier RLD labeling stated "Protect from light." However, newer labels do not have this statement. Also, in a previous review for another ANDA, the comment was made in the FTR that if packaged with nitrogen, the statement was not required.

10. The firm is asked to use rather than n their labels and labeling to be consistent with the USP 23 monograph title. Likewise, rather than

The RLD has one revision in the box of warnings - "Supports rapid microbial growth" has been revised to read "Supports microbial growth". "Rapid" has been deleted. This does make sense based on the addition of um to retard growth. It is noted that this is not an antimicrobially preserved product under USP standards. To date, we have not received FPL for the 6-11/96 approved in draft for SCF labeling.

11. Gensia submitted an "IV Transfer Label". See p. 100072. I have never seen such an approved label for the RLD. No comments will be made. We won't approve this.

12. BAIL BAND - We previously commented for the infusion vials that there is no indication that a plastic bail band or some other means is present to hang these vials for infusion. The firm replied in its 9-18-96 amendment (p. 10) that a bail band will be attached to the bottom of each infusion vial.

13. TO FILTER OR NOT TO FILTER?

    See FTR dated 28-Apr-1997, from Laurence Landow, re: Innovator being told to delete the statement "Do not use in-line filters with this product". It was also noted on a memo dated 28-Feb-1997 that the Division was to have sent a letter to the innovator to delete reference to the use of filters in the insert. Labels and labeling will be consistent to advise against the use of filters.

Date of Review: 10/20/ 1997 Dates of Submission: 3/31/1997

/S/ 10/20/97

Primary Reviewer: Julia Johnson Date: 10/20/97

Team Leader: Charles V. Hoppes Date:

/S/ 10/21/97

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
Gensia Laboratories, Ltd.	**3/31/97**
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NUMBER *(Include Area Code)*
19 Hughes **Irvine, CA 92618**	**(714) 457-4709**
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(if previously issued)* **ANDA No. To be Assigned**

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Propofol Injectable Emulsion	**Diprivan®**

CODE NAME *(If any)*	CHEMICAL NAME
--	**2,6 - diisopropylphenol**

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Emulsion	**Intravenous**	**10 mg/mL**

PROPOSED INDICATIONS FOR USE
Propofol Injectable Emulsion is indicated for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:
74-816

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check One)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Diprivan®	**Zeneca, Ltd.**

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

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JUL 1 1997
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SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g. Part 314.70 (B)(2)(iv)) Part 314.92

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

100001

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
X	2. Summary *(21 CFR 314.50 (c))*
X	3. Chemistry, manufacturing, and control section *(21 CFR 314.50 (d) (1))*
	4. a. Samples *(21 CFR 314.50 (e) (1))* (Submit only upon FDA's request)
X	b. Methods Validation Package *(21 CFR 314.50 (e) (2) (i))*
	c. Labeling *(21 CFR 314.50 (e) (2) (ii))*
X	i. draft labeling *(4 copies)*
	ii. final printed labeling *(12 copies)*
	5. Nonclinical pharmacology and toxicology section *(21 CFR 314.50 (d) (2))*
	6. Human pharmacokinetics and bioavailability section *(21 CFR 314.50 (d) (3))*
	7. Microbiology section *(21 CFR 314.50 (d) (4))*
	8. Clinical data section *(21 CFR 314.50 (d) (5))*
	9. Safety update report *(21 CFR 314.50 (d) (5) (vi) (b))*
	10. Statistical section *(21 CFR 314.50 (d) (6))*
	11. Case report tabulations *(21 CFR 314.50 (f) (1))*
	12. Case reports forms *(21 CFR 314.50 (f) (1))*
X	13. Patent information on any patent which claims the drug *(21 U.S.C. 355 (b) or (c))*
X	14. A patent certification with respect to any patent which claims the drug *(21 U.S.C. 355 (b) (2) or (j) (2) (A))*
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warning, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. **Good manufacturing practice regulations in 21 CFR 210 and 211.**
2. **Labeling regulations in 21 CFR 201.**
3. **In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.**
4. **Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.**
5. **Regulations on reports in 21 CFR 314.80 and 314.81.**
6. **Local, State and Federal environmental impact laws.**

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Donald J. Harrigan, R.Ph. **Director, Regulatory Affairs**	Donald J. Harrigan	**3/31/97**

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
19 Hughes, Irvine, CA 92618	**(714) 457-4709**

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

100002

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-102

CORRESPONDENCE

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

December 28, 1998

NEW CORRESP
NC to Fax

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's Abbreviated New Drug Application (ANDA 75-102) for Propofol Injectable Emulsion 1% containing 0.025% Sodium Metabisulfite. Reference is also made to the telephone conversation between Mr. Raymond Brown of the Agency and myself on December 28, 1998, in which Mr. Brown requested that Gensia Sicor reinstitute the Free Fatty Acid test and specification (NMT meq/mL) for the finished product.

Therefore, in accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, Gensia Sicor Pharmaceuticals, Inc., hereby amends this application and commits to incorporating the Free Fatty Acid test and specification for the finished product as specified by the Agency. We further commit to assuring that the addition requested by FDA will be reflected in the quality control and stability documentation prior to the commercial launch of this product. This documentation will be provided as a post-approval supplement.

GensiaSicor Pharmaceuticals • 17 Hughes • Irvine CA • 92618-1902 • USA
Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75102\AMENDS\AMEND15.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

December 21, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A F

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's Abbreviated New Drug Application (ANDA 75-102) for Propofol Injectable Emulsion 1% containing 0.025% Sodium Metabisulfite. Reference is also made to the Agency's facsimile dated December 21, 1998.

Therefore, in accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, Gensia Sicor Pharmaceuticals, Inc., hereby amends this application and commits to incorporate the labeling revisions specified in the Agency's facsimile dated December 21, 1998. We further commit to assuring that the revisions requested by FDA will be reflected in the labeling utilized for the commercial launch of this product.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75102\AMENDS\AMEND14.WPD
cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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GENERIC DRUGS

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NDA DRUG AMENDMENT
AC

December 28, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's Abbreviated New Drug Application (ANDA 75-102) for Propofol Injectable Emulsion 1% containing 0.025% Sodium Metabisulfite. Reference is also made to the telephone conversation between Mr. Raymond Brown of the Agency and myself on December 28, 1998, in which Mr. Brown requested that Gensia Sicor reinstitute the Free Fatty Acid test and specification (NMT neq/mL) for the finished product.

Therefore, in accordance with the provisions of Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, Gensia Sicor Pharmaceuticals, Inc., hereby amends this application and commits to incorporating the Free Fatty Acid test and specification for the finished product as specified by the Agency. We further commit to assuring that the addition requested by FDA will be reflected in the quality control and stability documentation prior to the commercial launch of this product. This documentation will be provided as a post-approval supplement.

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Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO751C2\AMENDS\AMEND15.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
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December 15, 1998

NEW JERSEY

NC

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Propofol Injectable Emulsion containing 0.025% Sodium Metabisulfite in the formulation, ANDA 75-102, submitted January 16, 1998.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to update the exclusivity statement.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

RECEIVED

DEC 16 1998

GENERIC DRUGS

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor Pharmaceuticals • 17 Hughes • Irvine CA • 92618-1902 • USA
Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

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December 14, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA [illegible] AMENDMENT
N/A F

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Propofol Injectable Emulsion containing 0.025% Sodium Metabisulfite in the formulation, ANDA 75-102, submitted January 16, 1998. Reference is also made to the Agency's facsimile dated December 11, 1998.

In accordance with the provisions of Section 314.96 of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the change in labeling as requested.

Please note that a number of changes to the package insert requested by the Agency were not required. Specifically, we did not incorporate the deletion of the text in the insert as identified in sections b. and c.(ii). After careful review of our labeling, we determined that this text does not appear in the last revision of our package insert for the propofol vial products.

Furthermore, we did not add the text to the insert as identified in section c.(iii). Upon review of our previous revision of the package insert, we determined that this text had already been incorporated.

RECEIVED
DEC 15 1998
[illegible]

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or Mr. Dwain K. Allen at (949) 457-2861. We may also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75102\AMENDS\AMEND12.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

November 10, 1998

Desk Copy
for
Mr. Peter Rickman

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDC

RE: ANDA 75-102
Propofol Injectable Emulsion 1%
Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

At this time we wish to notify the Agency of the legal actions taken by Zeneca Ltd. against Gensia Sicor regarding the Paragraph IV Patent Certification for Gensia Sicor's Propofol Injectable Emulsion 1% containing 0.025% Sodium Metabisulfite (ANDA 75-102).

In accordance with the provisions of Section 314.107(f)(2) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to inform the Agency of the legal actions taken by Zeneca Ltd. On April 3, 1998, Zeneca Ltd. initiated a patent infringement suit (patent 5,714,520) against Gensia Sicor in the United States District Court for the District of Delaware (Zeneca Limited v. Gensia Sicor Pharmaceuticals, Inc., Civil Action No. 98-170). On April 17, 1998, Zeneca dismissed the law suit. A copy of the initial action and the subsequent dismissal are provided in **Attachment 1** and **Attachment 2**, respectively.

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

Attachments

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

GensiaSicor™
PHARMACEUTICALS
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August 24, 1998

VIA FACSIMILE AND FEDERAL EXPRESS

Mr. Gordon Johnston
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Confidential Communication
Contains Proprietary Information
Exempt from Disclosure under
the Freedom of Information Act

RE: Propofol Injectable Emulsion
Alternative Preservative System
ANDA 75-102

Dear Mr. Johnston:

Reference is made to Gensia Sicor's correspondence dated July 17, 1997, in which we requested the FDA's evaluation of an alternate Propofol formulation utilizing sodium metabisulfite as the preservative agent. Reference is also made to our response to the Agency dated June 15, 1998, regarding the adult exposure levels of sulfites expected under the ICU indication, when a patient receives the proposed formulation of Propofol Injectable Emulsion in combination with total parenteral nutrition (TPN) products that also contain sulfites. Further reference is made to the recent telephone conference on August 19, 1998, between Gensia Sicor and the Office of Generic Drugs to discuss additional information relative to the safety of sodium metabisulfite as a preservative in our proposed product.

As a result of the telephone conference, we wish to provide additional information to support the safety of sodium metabisulfite as a preservative in our proposed formulation of Propofol Injectable Emulsion. Specifically, we wish to address the following issues that were raised during this conference:

1) The potential for sulfite hypersensitivity reactions occurring from the sodium metabisulfite contained in our formulation of Propofol.

2) Pediatric dose exposure levels of sulfites expected for the proposed formulation of Propofol as indicated in anesthesia maintenance when compared to sulfite-containing TPN products.

3) Pediatric dose exposure levels of sulfites expected for the proposed formulation of Propofol as indicated in anesthesia induction when

compared to other sulfite-containing injectable products.

4) A comparison of adult and elderly dose exposure levels of sulfites expected from more immediate administration (i.e., dose administered within 1 minute) of the proposed formulation of Propofol and other sulfite-preserved injectable products.

5) A comparison of risk between the preserving agents that is used in Zeneca's Diprivan (propofol) Injectable Emulsion, and sodium metabisulfite, that is used in Gensia Sicor's formulation of Propofol Injectable Emulsion.

Sulfite Hypersensitivity

Sulfite hypersensitivity is an adverse reaction associated with food and drug products preserved with sulfite agents. In the 1970's and 1980's, FDA received several case reports of adverse reactions to sulfite additives from foods and drugs. The reported adverse reactions included wheezing, bronchospasm, dyspnea, stomach cramps, flushing, hypotension, urticaria, and anaphylaxis.[1] In 1986, Celeste reported that FDA was aware of approximately 500 reports of adverse reactions to sulfites in foods, including 12 fatal cases allegedly involving sulfites. Adverse reactions to drugs containing sulfites were also reported. FDA noted that the adverse reactions appeared to be relegated to a sub-population of asthmatics; and to a rare number in the non-asthmatic population. In response to the reports of hypersensitivity reactions associated with sulfites, FDA took three separate regulatory actions. In August 1986, FDA promulgated a regulation to ban the use of sulfites in fresh fruits and vegetables.[2] In another regulation, the Agency required packaged foods containing sulfites to be labeled if sulfites are present at levels equal to or greater than 10 ppm.[3] The third regulatory action in June 1987 was to amend the drug labeling regulations to require a

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[1] Celeste, A. Update on Sulfites. *Assoc. Food Drug U.S. Off. Q. Bull.* 50:46, 1986. (As reported in Gunnison, A.F. & Jacobsen, D.W. Sulfite Hypersensitivity: A Critical Review. *CRC Critical Reviews in Toxicology.* 17 (3):185-214, 1987.)

[2] Sulfiting agents: revocation of GRAS status for use on fruits and vegetables intended to be served or sold raw to consumers. *Federal Register*, 51 (131):25021-25026, July 9, 1986.

[3] Food labeling: declaration of sulfiting agents. *Federal Register*, 51 (131):25012-250206, July 9, 1986.

sulfite warning in the package insert of drug products containing sulfite preservatives.[4] The Agency's actions were taken to safeguard, in particular, the hypersensitive asthmatic sub-population.

According to Gunnison and Jacobsen, approximately 5-10% of all asthmatics are sulfite hypersensitive.[5] Of the nearly 14.6 million Americans with asthma as estimated in 1994,[6] this translates to a sub-population of 0.73 - 1.46 million asthmatics who are possibly reactive to sulfites and, in general, represents 0.3 - 0.6% of the U.S. population.[7] According to Gunnison and Jacobsen, chronic asthma is the predominant predisposing factor that leads to sulfite hypersensitivity.[5]

It is suggested that sulfite oxidase deficiency in chronic asthmatics may play a role in the sulfite hypersensitivity. Specifically, chronic asthmatics with sulfite oxidase deficiency may be unable to adequately metabolize exogenous sulfites. However, the mechanism by which systemic sulfites trigger a hypersensitivity reaction is not yet know. From the review of several studies involving provocative challenge protocols and case reports of individual patients as summarized by Gunnison and Jacobsen, the hypersensitivity reaction to sulfites does not appear to be dose-related, but represents an idiosyncratic response.[5] Variations in the dose and route of administration appear to elicit varying degrees of reaction in different individuals.

In general, exogenous sulfites are rapidly oxidized to sulfate via sulfite oxidase and secreted in the urine as sulfate. The capacity of sulfite oxidase for sulfite oxidation is extremely high compared with the normal sulfite load from exogenous and endogenous sources. Because of its rapid metabolic clearance, sulfite does not accumulate in the tissues. Usually, no free sulfite is detected in plasma. Free sulfite has been reported in the plasma of a child diagnosed as deficient in sulfite oxidase.[8]

Furthermore, sedation does not affect the elimination of sulfite. This is supported by the similar sulfite clearance in a rhesus monkey while sedated as compared to normal

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[4] Sulfiting agents: labeling in drugs for human use, warning statement. *Federal Register*, 51 (234):43900-43904, December 5, 1986.

[5] Gunnison, A.F. & Jacobsen, D.W. Sulfite Hypersensitivity: A Critical Review. *CRC Critical Reviews in Toxicology*. 17 (3):185-214, 1987.

[6] *Vital and Health Statistics*. Series 10, No. 193

[7] Based upon U.S. population of 265.3 million in 1996 by the U.S. Census Bureau.

[8] Gunnison, A. F. Sulphite Toxicity: A Critical Review of In-Vitro and In-Vivo Data. *Food and Cosmetic Toxicology*. 19: 667-682, 1981.

experimental conditions.[9] Therefore, we believe that Propofol Injectable Emulsion with sodium metabisulfite will be well tolerated over an extended period, and also the clearance of sodium metabisulfite will not be affected by the action of Propofol.

In relation to the sodium metabisulfite added to our formulation of Propofol Injectable Emulsion, Gensia Sicor recognizes the potential risk of sulfite hypersensitivity reactions by this sub-population of asthmatics, and in rare cases, a sub-population of non-asthmatics. We believe this risk is mitigated by the application of the FDA-required warning statement for sulfites on the drug labeling. The warning is intended to alert health care practitioners of the risk to patients with *known* hypersensitivity to sulfites.

In the event the hypersensitivity is not disclosed in the course of the patient's history, and a reaction is manifested following the administration of Gensia Sicor's Propofol product, the patient will present with the reaction in a hospital setting, pursuant to the indications, to allow immediate medical measures to be taken. The key indices of the sensitivity reaction are wheezing and bronchospasm in the asthmatic. Both reactions are readily identifiable by the clinician (even when the patient is under anesthesia) such that treatment can be initiated immediately.

Propofol Pediatric Dose for Maintenance of General Anesthesia - Exposure Levels of Sulfites from Propofol Compared to TPN Products

To determine pediatric dose exposure levels of sulfites resulting from the administration of Gensia Sicor's formulation of Propofol as indicated in anesthesia maintenance and compared to sulfite-containing TPN products, we have performed an evaluation for pediatric patients assuming standard weights for a newborn (3.5 kg), an infant (12 kg), and a child (30 kg). It should be noted that **Propofol is not recommended for administration to children less than 3 years old nor is the product recommended for ICU or MAC sedation in children, in general. Propofol is only indicated for general anesthesia in children age 3 years and older.** Although the sulfite exposure due to TPN products in children (≥ 3 years) is of most interest for the purposes of direct comparison to sulfite doses resulting from administration of Propofol, information regarding the sulfite exposure levels from TPN products in newborns and infants are also presented as a point of interest.

For a pediatric patient 3 years of age or older undergoing maintenance of general anesthesia, the theoretical levels of sulfite exposure expected from the administration of Gensia Sicor's sodium metabisulfite formulation of Propofol is expected to be 13.5 mg/hr. We arrived at a theoretical hourly amount of sodium metabisulfite based upon a maintenance dose for general anesthesia of 18 mg/kg/hr of Propofol, assuming a standard weight pediatric patient of 30 kg, i.e.,

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[9] Gunnison et al. Comparative Sulfite Metabolism in the Rat, Rabbit, and Rhesus Monkey. *Toxicology and Applied Pharmacology.* 42: 99-109, 1977.

(18 mg/kg/hr) X (30 kg) X [(0.25 mg/mL SMBS)/(10 mg/mL Propofol)]

= 13.5 mg SMBS/hr.

Table 1 summarizes information from *Facts and Comparison* (1997),[10] which lists the amounts of sulfite preservatives contained in various amino acid solutions and the relation to pediatric product doses in newborns, infants, and children. The dosage information for each TPN product is based upon the *pediatric* TPN protocols described in *Facts and Comparison* (1997).[10] This table further summarizes the amount of sulfite exposure expected.

Table 1

Product	Preservative	Preservative Dose (mg/hr)*		
		Newborn (3.5 kg)	Infant (12 kg)	Child (30 kg)
Aminosyn II 5% (Abbott)	20 mg/dL Sodium Hydrosulfite	2.2	7.5	19
Aminosyn II 10% (Abbott)	20 mg/dL Sodium Hydrosulfite	1.1	3.8	9.4
Aminosyn-PF 10% (Abbott)	230 mg/100 mL Sodium Hydrosulfite	13	43	108
Aminosyn 15% (Abbott)	60 mg/100 mL Sodium Hydrosulfite	2.2	7.5	19
TrophAmine 6% (McGaw)	< 50 mg/100 mL Sodium Metabisulfite	4.6	16	39
TrophAmine 10% (McGaw)	< 50 mg/100 mL Sodium Metabisulfite	2.7	9.4	23
FreeAmine III 8.5% (McGaw)	<0.1 g/100 mL Sodium Bisulfite	6.4	22	55
FreeAmine III 10% (McGaw)	<0.1 g/100 mL Sodium Bisulfite	5.5	19	47
Novamine 15% (Abbott)	30 mg/100 mL Sodium Bisulfite	1.1	3.8	9.4
Aminosyn-RF 5.2% (Abbott)	60 mg/100 mL Sodium Metabisulfite	6.3	22	54
NephrAmine 5.4% (McGaw)	< 0.05 g/100 mL Sodium Bisulfite	5.1	17	43
HepatAmine 8% (McGaw)	< 100 mg/100 mL Sodium Bisulfite	NP**	NP	59

* TPN Pediatric Protocol: 150 mL/kg/day of a 2.5% Amino Acid solution (equivalent to 3.75 g/kg/day)
** NP = Not Provided

[10] For the specific list of page references for each drug product discussed, refer to **Attachment 1.**

For children 3 years of age or older, TPN solutions were determined to yield sulfite preservative doses (up to 108 mg/hr), in general, greater than or equivalent to the theoretical level of exposure (13.5 mg/hr) from Propofol containing sodium metabisulfite, when administered for pediatric anesthesia maintenance. Additionally, the sulfite exposure for newborns (up to 13 mg/hr) and infants (up to 43 mg/hr) when receiving TPN products are also in the range of the 13.5 mg/hr exposure experienced by a pediatric patient (≥ 3 years) receiving Gensia Sicor's formulation of Propofol. It is important to note that Aminosyn-PF 10% is marketed specifically for pediatric administration and, in this evaluation, represents the highest dose of sulfite (108 mg/hr) to the pediatric patient 3 years of age and older in comparison to other TPN products.

In certain clinically compromised states, TPN products containing sulfites are indicated for pediatric administration. Specifically, Aminosyn-RF 5.2% and NephrAmine 5.4% are indicated for treatment of renal failure; and HepatAmine is specially formulated for the treatment of hepatic failure/hepatic encephalopathy. Pediatric patients (≥ 3 years) receiving these TPN solutions are exposed to sulfites of 43 to 54 mg/hr, which is in excess of the expected sulfite exposure of 13.5 mg/hr when our proposed formulation of Propofol is administered. Based upon the pediatric dose contributed from approved TPN products in the most compromised patients, it is expected that the levels of sulfite from Gensia Sicor's formulation of Propofol should be well tolerated in both health and compromised patients.

In conclusion, the total contribution of sulfite from amino acid TPN products for pediatric indications correlates to levels of sulfite expected to be safe for administration of Gensia's Propofol Injectable Emulsion for pediatric maintenance anesthesia.

Propofol Pediatric Dose for Induction of General Anesthesia - Exposure Levels of Sulfites from Propofol Compared to Other IV Products

For a comparison of immediate administration (i.e., dose administered within 1 minute), theoretical levels of sulfite exposure expected for pediatric patients receiving parenteral products containing sulfites were compared to sulfite levels expected to be contributed by Gensia Sicor's formulation of Propofol based upon the pediatric dosing for induction of general anesthesia. For purposes of this analysis, pediatric dosing will focus upon children 3 years or older, however, information for newborns and infants is also of interest. The evaluation includes the overall scope of sulfite exposure to pediatric patients from two approved drug products, Gallamine Triethiodide (20 mg/mL) and Tubocurarine Chloride (3 mg/mL). As in the previous section, the assumption for pediatric standard weights remains the same. Since Propofol is not recommended for administration to children less than 3 years old, comparison to short term exposure to sulfites in children 3 years of age or older is of greatest value.

For a pediatric patient 3 years of age or older, the theoretical levels of sulfite exposure expected from the administration of the Gensia Sicor's sodium metabisulfite formulation of Propofol for induction of general anesthesia (i.e., per labeling, 2.5 - 3.5 mg/kg over

20 - 30 sec.) have been calculated. The theoretical amounts of sodium metabisulfite based upon dosing for induction were determined as follows:

Induction

(2.5 - 3.5 mg/kg) X (30 kg) X [(0.25 mg/mL SMBS)/(10 mg/mL Propofol)]

= 1.9 - 2.6 mg SMBS in 20 to 30 sec.

Review of *Facts and Comparison* (1997)[11] for other products containing sulfites which list pediatric dosing protocols provided two drugs used as adjuncts to anesthesia: Gallamine Triethiodide (20 mg/mL) and Tubocurarine Chloride (3 mg/mL). These two products compare well to Gensia Sicor's Propofol, because both contain the same sulfite preservative, sodium metabisulfite, and both are used in a surgical setting. The levels of sodium metabisulfite exposure from these products based upon the pediatric protocols are provided in **Table 2** below:

Table 2

Product	Preservative	Method of Administration	Preservative Dose (mg)		
			Newborn (3.5 kg)	Infant (12 kg)	Child (30 kg)
Gallamine Triethiodide, 20 mg/mL (Davis + Geck)	2.5 mg/mL Sodium Metabisulfite	*Initial: 1.5 mg/kg* *Repeat: 1 mg/kg after 30-40 min. as needed*			
		Initial Dose	0.66	2.3	5.6
		Repeat Dose	0.44	1.5	3.8
Tubocurarine Chloride, 3 mg/mL (Abbott)	1 mg/mL Sodium Metabisulfite	*Neonates: 0.3 mg/kg* *Children: 0.6 mg/kg* *Sustained injection in 1-1.5 min.*			
		Initial (1 min.)	0.35	2.4	6.0
		Repeat Dose	0.35	2.4	6.0

In pediatric protocols for immediate administration, the exposure level of sodium metabisulfite ranges from 3.8 to 6.0 mg for the two approved products, Gallamine Triethiodide and Tubocurarine Chloride. This range is comparable to the expected levels of sulfite from the dosing of Propofol with sodium metabisulfite during pediatric induction. Therefore, the sulfite exposure due to Propofol for pediatric induction would

[11] For the specific list of page references for each drug product discussed, refer to **Attachment 1**.

be expected to correlate with safe levels as supported by the two approved products.

Adult and Elderly Dose-Exposure Levels of Sulfites from Propofol Compared to Other IV Products

For a comparison of immediate administration in adult and elderly patients, theoretical levels of sulfite exposure expected for these groups receiving parenteral products containing sulfites were compared to sulfite levels expected from Gensia Sicor's formulation of Propofol. Comparisons were made based upon the recommended Propofol dosing for bolus injection, induction and maintenance for general anesthesia and MAC sedation. Information with regard to the dosing of the comparator products was obtained from *Facts and Comparison* (1997).

The levels of sulfite exposure from various injectable products as well as the sulfite exposure levels from Propofol were calculated for the adult and elderly indications. The theoretical amounts of sulfite for the Propofol and the comparator products are summarized in **Table 3** and **Table 4**, respectively.

Table 3

Product Description	Preservative Concentration	Method of Administration	Preservative Dose	
			Elderly (70 kg)	Adult (70 kg)
Propofol Injectable Emulsion, 1% (Gensia Sicor)	0.025% Sodium Metabisulfite	*General Anesthesia:* *Bolus injection - 50 mg per as required* *Elderly - 1.5 mg/kg for induction (10 sec)* *Maintenance @ 100 mcg/kg/min.* *Adult - 2.5 mg/kg for induction (10 sec)* *Maintenance @ 200 mcg/kg/min.*		
		Intermittent Bolus	12.5 mg	12.5 mg
		Induction	2.63 mg	4.38 mg
		Maintenance	10.5 mg/hr	21 mg/hr
		MAC Sedation: *Elderly - 0.5 mg/kg for induction (5 min)* *Maintenance @ 20% of 75 mcg/kg/min.* *Adult - 0.5 mg/kg for induction (5 min)* *Maintenance @ 75 mcg/kg/min.*		
		Induction	0.88 mg	0.88 mg
		Maintenance	6.3 mg/hr	7.9 mg/hr

Table 4

Product Description	Preservative Concentration	Method of Administration	Preservative Dose	
			Elderly (70 kg)	Adult (70 kg)
Gallamine Triethiodide, 20 mg/mL (Davis + Geck)	2.5 mg/mL Sodium Metabisulfite	*Adjunct to Anesthesia:* *Initial dose - Max of 100 mg* *Repeat dose - 1 mg/kg every 30-40 min as needed*		
		Initial Dose	12.5 mg	12.5 mg
		Repeat Dose	8.75 mg	8.75 mg
Tubocurarine Chloride, 3 mg/mL (Abbott)	1 mg/mL Sodium Metabisulfite	*Adjunct to Anesthesia:* *Initial dose - sustained injection of 0.6 mg/kg* *Repeat dose - 0.6 mg/kg every 30-40 min. as needed*		
		Initial (1 min.)	14 mg	14 mg
		Repeat Dose	14 mg	14 mg
Intropin (dopamine), 40 mg/mL (Faulding)	1% Sodium Metabisulfite	*Vasopressor in Shock:* *Elderly - calculated using lower dose of 2 mcg/kg/min.* *Adult - calculated using upper dose of 50 mcg/kg/min.*		
		IV Infusion	2.1 mg/hr	52.5 mg/hr
Epinephrine, 0.1 mg/mL (Abbott)	0.46 mg/mL Sodium Metabisulfite	*Vasopressor for Resuscitation: 1 mg every 5 min.*		
		Bolus every 5 min	4.6 mg	4.6 mg
Hydrocortisone Sodium Phosphate, 50 mg/mL (MSD)	3.2 mg/mL Sodium Bisulfite	*Adrenal Cortical Steroids:* *Elderly - calculated using lower dose of 15 mg/day* *Adult - calculated using upper dose of 240 mg/day*		
		Dosed every 12 hrs	0.32 mg	5 mg
Aminosyn-PF 10% (Abbott)	230 mg/100 mL Sodium Hydrosulfite	*500 mL/8 hr*		
		TPN	144 mg/hr	144 mg/hr

Table 5 below summarizes the our assessment of other parenteral drugs with comparable sulfite exposure levels correlated to the methods of administration for Propofol Injectable Emulsion to adult and elderly patients.

Table 5

Propofol Injectable Emulsion Method of Administration		**Other Parenteral Drugs with Comparable Sulfite Exposure Levels**
General Anesthesia in Elderly and Adult		
Intermittent Bolus	12.5 mg	Range: 12.5 - 14 mg Gallamine Triethiodide Tubocurarine Chloride
Induction	2.6 mg & 4.4 mg	Range: 4.6 - 14 mg Gallamine Triethiodide Tubocurarine Chloride Epinephrine Hydrocortisone Sodium Phosphate
Maintenance	10.5 mg/hr & 21 mg/hr	Range: 53 - 144 mg/hr Intropin (dopamine) Total Parenteral Nutrition Products (Amino Acids)
MAC Sedation in Adult and Elderly		
Induction	0.88 mg	Range: 4.6 - 14 mg Gallamine Triethiodide Tubocurarine Chloride Epinephrine Hydrocortisone Sodium Phosphate
Maintenance	6.3 mg/hr & 7.2 mg/hr	Range: 53 - 144 mg/hr Intropin (dopamine) Total Parenteral Nutrition Products (Amino Acids)

Based upon our assessment provided in **Table 4** and the data summarized in **Table 3**, the safety of sulfite exposure for adult and elderly patients when administered Propofol by intermittent bolus (12.5 mg), induction for general anesthesia (2.6 - 4.4 mg), and induction for MAC sedation (0.88 mg) are supported by the exposure levels which range from 4.6 to 14 mg for the approved products evaluated. When examining the sulfite exposure levels for patients administered propofol for the maintenance of general anesthesia and MAC sedation, our product is expected to deliver 6.3 - 21 mg/hr of sulfite compared to 53 - 144 mg/hr for the approved products.

Therefore, the sulfites levels due to adult and elderly doses of our proposed Propofol when used in general anesthesia and MAC sedation are equivalent or lower to sulfite

levels expected for previously approved products.

Risk Assessment - Sodium Metabisulfite vs. EDTA

As previously discussed in the section, "Sulfite Hypersensitivity," the risk is well known and well recognized as established by FDA in the 1980's. The safety of Propofol with sodium metabisulfite for long term administration is supported by the extended use of sulfite-containing amino acid TPN products. From the previous discussions, we determined that the sulfite exposure levels from Gensia Sicor's' Propofol would be less than levels contributed by the TPN products evaluated. Based upon sulfite exposure levels expected from administration of our Propofol for general anesthesia, equivalent sulfite exposure levels were determined from the dosing of approved drugs, specifically, Gallamine and Tubocurarine. In addition, the regulatory requirement to include the warning statement mitigates the risk associated with sulfites. The clinician is alerted to the potential effects of sulfites via the labeling. Since Propofol is administered for purposes of surgery, MAC sedation, or ICU sedation in a hospital setting under continuous medical monitoring, the patient is assured of immediate medical attention should a hypersensitivity reaction occur.

Sulfite preservatives are included in the formulations of many FDA-approved drug products.[12] In December 1986, FDA disagreed with a complete prohibition of the use of sulfites, however acknowledged that people should be provided sufficient information to avoid sulfites. Gensia Sicor is aware that sodium metabisulfite presents an inherent risk, especially to an asthmatic sub-population, as an additive in formulation of Propofol Injectable Emulsion. However, the limited preservative effect resulting from the presence of sodium metabisulfite accede to health benefits of the general public and outweigh the risk of sulfite hypersensitivity.

EDTA is also an inactive ingredient included in the formulations of many FDA-approved drug products. However, at the levels indicated in Zeneca's Diprivan (propofol) Injectable Emulsion with 0.005% EDTA, FDA recognized a potential risk of zinc depletion and mild renal damage due to long term exposure to EDTA from administration of Diprivan Injectable Emulsion for ICU use.[13, 14] Due to these potential risks, Zeneca was requested to add the following warning statement to the Diprivan

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[12] *Inactive Ingredient Guide (January 1996).* Division of Drug Information Resources, Office of Management, CDER, FDA.

[13] I.L. Tyler, Ph.D., M.D. Medical Officer Review NDA Report Propofol with 0.005% EDTA. Summary Basis of Approval for Diprivan Injectable Emulsion with 0.005% EDTA.

[14] Robert F. Bedford, M.D. Medical Officer Secondary Review. Summary Basis of Approval for Diprivan Injectable Emulsion with 0.005% EDTA.

product insert as follows:

> EDTA is a strong chelator of trace metals - including zinc. Calcium disodium edetate has been used in gram quantities to treat heavy metal toxicity. When used in this manner it is possible that as much as 10 mg of elemental zinc can be lost per day via this mechanism. Although with Diprivan Injectable Emulsion there are no reports of decrease 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.
>
> At high doses (2 - 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.[15]

In addition due to FDA's concern regarding the potential risks of extended exposure to EDTA in an ICU setting, FDA informed Zeneca that approval of the EDTA formulation of Diprivan would be predicated upon a commitment from the company to perform a Phase IV Safety study to evaluate zinc loss and renal function in ICU patients.

In summary, sodium metabisulfite as an additive in parenteral drug products presents a known but limited risk of producing a hypersensitivity reaction, predominantly in chronic asthmatics. EDTA as an additive in an injectable at the levels defined in Zeneca's formulation of Diprivan presents an unknown risk. However, we understand that a phase IV safety study was requested by FDA to determine the level of risk associated with this exposure level of EDTA. The potential risks recognized by FDA are zinc depletion and mild renal damage. We trust that FDA is monitoring Zeneca for compliance with Zeneca's phase IV commitments.

Conclusion

We trust that the information provided herein, in conjunction with the information submitted to the Agency in correspondence dated July 17, 1997, June 15, and June 20, 1998, is adequate to support the Agency's decision that the substitution of sodium metabisulfite for edetate disodium as the preservative in our Propofol Injectable Emulsion does not affect the safety of our proposed product.

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[15] Warnings section of package insert of Diprivan Injectable Emulsion with 0.005% EDTA.

Should you have any questions or would like to further discuss this matter, please do not hesitate to contact me at (949) 455-4716. We will call you on Wednesday, August 26, to follow up on your meeting with the Office of New Drug Evaluation regarding this matter.

Sincerely,

Armand J. LeBlanc
Vice President, Scientific Affairs

Attachments

cc: Mr. Donald B. Hare - Office of Generic Drugs
Dr. Cynthia McCormick - Anesthetic, Critical Care & Addiction Drug Products
Dr. Roger Williams - Pharmaceutical Science

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McDERMOTT, WILL & EMERY

August 10, 1998

CONFIDENTIAL

NEW CORRESP

VIA FACSIMILE AND FEDERAL EXPRESS

ANDA 75-102

Mr. Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Metro Park North II
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: Telephone Conference with GensiaSicor Pharmaceuticals, Inc. Regarding the Use of Sodium Metabisulfite as a Preservative in its Propofol Injectable Emulsion, 10mg/mL

Dear Mr. Sporn:

I am writing to you on behalf of our client, GensiaSicor Pharmaceuticals, Inc. to request and confirm telephone conference with representatives of the Office of Generic Drugs ("OGD") and Dr. Roger Williams of the Office of Pharmaceutical Science to present and discuss additional information supporting the conclusion that the difference in preservative used by GensiaSicor does not affect the safety of the proposed product.

GensiaSicor is requesting that the teleconference be scheduled before August 25, the date on which I understand that there will be a meeting of CDER staff to discuss this matter. The additional information to be presented and discussed further supports the material previously submitted by GensiaSicor that the substitution of sodium metabisulfite for edetate sodium as a preservative does not affect the safety of Propofol Injectable Emulsion.

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AUG 12 1998
GENERIC DRUGS

As this matter is of the utmost importance to GensiaSicor, we appreciate your accommodation of this request. I will call you later this week to arrange a date and time for the telephone conference.

Attendees. The following people will participate in the telephone conference:

GensiaSicor Pharmaceuticals, Inc.

Armand J. LeBlanc, Vice President, Scientific Affairs

Rosalie Lowe, Associate Director, Regulatory Affairs

Consultants

Meeting Agenda. The proposed agenda for the telephone conference is as follows:

1. Brief Introduction

2. Review of the Difference in Preservative Systems Between the GensiaSicor and Reference Listed Product

3. Review of Safety and Clinical Impact Concerning the Use of Sodium Metabisulfite as a Preservative in Propofol Injectable Emulsion

4. Discussion of GensiaSicor's ANDA

I appreciate your assistance in arranging the telephone conference and look forward to the discussion. Again, I will call you later this week to confirm the date and time for telephone conference. Of course, please do not hesitate to call me at (202) 756-8075 if you need any further information.

Sincerely yours,

David L. Rosen

cc: Armand J. LeBlanc
Rosalie Lowe
GensiaSicor Pharmaceuticals, Inc.

Rita Hassall, OGD
Gordon Johnston, OGD
Ted Sherwood, OGD

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NEW CORRESP

June 30, 1998

CONFIDENTIAL
Exempt from Disclosure Under FOIA

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion, 10 mg/mL
Containing 0.025% Sodium Metabisulfite
Technical Response to Citizens Petition 98P-0221/PSA 1

GENERAL CORRESPONDENCE

Dear Mr. Sporn:

Reference is made to Docket No. 98P-0221/PSA 1, the citizens petition (the "Petition") submitted by Stephen Mahinka, Esq., counsel to Zeneca Inc., to stay the effective date of pending, tentative, or final decisions to approve ANDAs for certain generic versions of Diprivan® (Propofol) Injectable Emulsion.

We have provided a "General Response" to the Petition which was submitted to the Dockets Management Branch on June 30, 1998, to support the position that the Commissioner deny the Petitioner's request (a copy of this response is enclosed as **Attachment 1**). This "General Response" provides adequate justification for the Commissioner to deny the Petitioner's request. However, in the "General Response" we have not addressed the specific technical issues related to our sodium metabisulfite formulation of propofol. As you know, Gensia Sicor has submitted paragraph IV certification in this ANDA. In addition, Gensia Sicor has sent notice to Zeneca stating that, in our opinion, and to best of our knowledge, our Propofol Injectable Emulsion with a preservative other than EDTA does not infringe Zeneca's patents pertaining to Diprivan® with EDTA. In such notices to Zeneca, we have not disclosed the preservative used in our product. Consequently, due to the confidential nature of this information, Gensia Sicor has decided to respond to these technical issues within our

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CONFIDENTIAL

ANDA. Therefore, the information contained within this submission will provide the Agency with Gensia Sicor's position with respect to the technical issues brought forth in the aforementioned Petition.

Furthermore, since this technical response contains confidential, commercial, and trade secret information and data, in our opinion, it is exempt from public disclosure. Should you believe otherwise, we request that you notify us prior to disclosing any information concerning the preservative in our propofol product.

Clearly, the Petitioner and Zeneca are once again attempting to block entry of a legitimate generic product in an effort to maintain Zeneca's monopoly of the propofol market. This is evidenced by the fact that the Petition does not direct the Agency to undertake any additional administrative action beyond those defined within the existing statutes and regulations. Pursuant to these statutes and regulations, FDA will appropriately rule to approve or deny an application based upon relevant scientific review of the application to determine the safety and efficacy of a drug product. However, we recognize that the Petition provides points-to-consider with respect to review of an application for a propofol formulation containing an alternate preservative. It is to these specific points that we wish to respond.

Gensia Sicor wishes to defend its application in light of the issues raised by the Petitioner. Accordingly, we request the opportunity to meet with the Agency to discuss these latest developments no later than July 31, 1998. I will call your office next week to arrange a mutually convenient date and time for the meeting. In the interim, if additional information is required or if there are any questions concerning this matter, please do not hesitate in contacting me at (949) 455-4716.

Sincerely,

Armand J. LeBlanc
Vice President, Scientific Affairs

Enclosure

cc: Mr. Gordon Johnson
Mr. Don Hare
Mr. Peter Rickman
Office of Generic Drugs

Ms. Elaine Messa
Los Angeles District

Ms. Paula Botstein, MD
Office of Drug Evaluation III

Ms. Cynthia McCormick, MD
Division of Anesthesiology, HFD 170

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NEW CORRESP

May 27, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion, 10 mg/mL
Formulation Containing 0.025%
Sodium Metabisulfite

RECEIVED
MAY 28 1998
GENERIC DRUGS

AMENDMENT

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application for Propofol Injectable Emulsion containing 0.025% Sodium Metabisulfite, ANDA 75-102. Further reference is made to the two amendments, which contained Paragraph IV Patent Certification Statements, dated February 11, 1998 and April 13, 1998.

In accordance with the provisions of Section 314.95(e) of the *Code of Federal Regulations, Title 21*, we hereby amend this application. We wish to document receipt of the notices as required under paragraph (a) of Section 314.95 by three of the four entities provided the notices. Copies of the return receipts are attached. Please note that the Return Receipt requested of the U.S. Postal Service (USPS) for the notice regarding Patent No. 5,714,520, which was sent to Zeneca Ltd. in the United Kingdom on February 11, 1998, has not been returned. A trace to locate the document was placed with the USPS on April 17, 1998, however, USPS has been unsuccessful in obtaining the Return Receipt to date. Therefore, it is our contention that Zeneca Ltd. received adequate notice since a Return Receipt was received from Zeneca Inc. in Wilmington, Delaware. In addition, Zeneca formally responded to our notice by filing a lawsuit on April 3, 1998, which was subsequently withdrawn.

GensiaSicor Pharmaceuticals • 17 Hughes • Irvine CA • 92618-1902 • USA
Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

We trust you will find the attached documentation satisfactory. Should you have any questions or require further clarification, please contact me at (949) 457-2808 or by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

Attachments
S:\PRO75102\AMENDS\AMEND8.WPD

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

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VIA FACSIMILE AND FEDERAL EXPRESS MAIL

NEW CORRESP NAI 4/20/4

April 13, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion, 10 mg/mL
Formulation Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia's Abbreviated New Drug Application (ANDA 75-102) for Propofol Injectable Emulsion containing 0.025% Sodium Metabisulfite.

At this time we wish to submit a updated Patent/Exclusivity Statement which provides a certification statement regarding the two patents granted Zeneca Ltd. on March 24, 1998, for Diprivan®. The referenced information was obtained on April 3, 1998, from FDA's web site at http://www.fda.gov/cder/orange/docket.pdf.

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APR 14 1998
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We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (714) 455-4724 or by facsimile at (714) 583-7351. (Please be advised that our area code will change from "714" to "949" on April 18, 1998.)

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Associate Director, Regulatory Affairs

Enclosure

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

Mr. Peter Rickman
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-615
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

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March 12, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion, 10 mg/mL
Formulation Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia Sicor's amendment to ANDA 75-102 for Propofol Injectable Emulsion (with 0.025% Sodium Metabisulfite), 10 mg/mL, which was submitted January 16, 1998. Reference is also made to a telephone conversation on February 12, 1998, between Mr. Ray Brown, Chemistry Reviewer in the Office of Generic Drugs, and myself regarding the submission of referenced information from ANDA 74-816. Mr. Brown's request is intended to consolidate all relevant information within a single application. As agreed, we have provided all sections of the ANDA 75-102 which previously included references to ANDA 74-816.

Therefore, in accordance with Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby amend this application (ANDA 75-102) for Propofol Injectable Emulsion (with 0.025% Sodium Metabisulfite), 10 mg/mL, with additional information. These revised sections provided herein supersede all previous information submitted for these specific sections of the ANDA.

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Phone (714) 455-4700, (800) 729-9991 • Fax (714) 855-8210 • http://www.gensiasicor.com

The sections listed below were previously referenced by incorporation and were not included in the amendment dated January 16, 1998. These sections are provided in this amendment.

Section IX	Description of Manufacturing Facility
Section X	Outside Firms Including Contract Testing Laboratories
Section XIII	Packaging and Labeling Procedures
Section XVIII	Control Numbers
Section XX	Environmental Impact Statement
Section XXI	Other

In addition, **Section XI** and **Section XVI** has been provided in their entirety. Please note that these sections were submitted previously, but included several references to ANDA 74-816.

Finally, **Section 3** of the Sterility Assurance Validation package has also been revised to include the information referenced in ANDA 74-816.

The amendment consists of two (2) volumes and has been formatted in accordance with the Office of Generic Drug's Policy and Procedure Guide #30-91 issued April 10, 1991; and, as modified by FDA's October 14, 1994 letter to all NDA, ANDA, and AADA applicants. Copies are provided as follows:

1) One (1) Archival Copy bound in Blue Jackets
2) One (1) Review Copy bound in Red Jackets

A true copy of this amendment, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration of Irvine, California, District Office.

Since **Section XVI** has been provided in its entirety, three (3) complete methods validation packages (i.e., packages which include information referenced in ANDA 74-816) have been included and are marked "Analytical Methods." These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting myself at (714) 457-2808.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

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NEW CORRESP
NC

February 11, 1998

VIA FACSIMILE AND FEDERAL EXPRESS MAIL

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-102
Propofol Injectable Emulsion, 10 mg/mL
Formulation Containing 0.025% Sodium Metabisulfite

AMENDMENT

Dear Mr. Sporn:

Reference is made to Gensia's Abbreviated New Drug Application (ANDA 75-102) for Propofol Injectable Emulsion containing 0.025% Sodium Metabisulfite. Reference is also made to a telephone conversation on February 2, 1998 between myself and Ms. Margo Bartel, Office of Generic Drugs, FDA, regarding the Patent/Exclusivity Statement provided in our application.

Ms. Bartel requested that Gensia Sicor amend its application for Propofol Injectable Emulsion (0.025% Sodium Metabisulfite) to include a certification statement for the new patent which was recently granted the innovator, Zeneca Ltd., for their formulation of propofol containing EDTA. Pursuant to Ms. Bartel's request, the Patent/Exclusivity Statement (Section III) has been revised and is included in this amend

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We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (714) 457-2808 or by facsimile at (714) 583-7351.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

S:\PRO75102\AMENDS\AMEND5\AMEND5.WPD
Enclosure

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

Mr. Peter Rickman
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-615
Attention: Documentation and Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

GENSIA
LABORATORIES LTD

December 3, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion (with 0.005% EDTA), 10 mg/mL Prefilled Syringe ANDA: 75-102

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Propofol Injectable Emulsion (Prefilled Syringe) containing 0.005% Disodium Edetate (EDTA) in the formulation, ANDA 75-102. Reference is also made to the Agency's letter dated October 22, 1997. In accordance with the provisions of Section 314.96 of the Code of Federal Regulations, Title 21, we hereby amend our application to provide the additional information as requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting Ms. Rosalie A. Lowe, Associate Director, Regulatory Affairs, at (714) 457-2808, or myself at (714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

Enclosure

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

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Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92618 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095

GENSIA
LABORATORIES, LTD.

NEW CORRESP

NC

May 20, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion
(with 10 mg/mL
Prefilled Syringe
ANDA: 75-102

AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Propofol Injectable Emulsion (Prefilled Syringe) containing e formulation, ANDA 75-102. Reference is also made to the Agency's letter dated May 8, 1997 regarding the Patent/Exclusivity Statement (Section III, Volume 1) provided in this application. In accordance with the provisions of Section 314.96 of the Code of Federal Regulations, Title 21, we hereby amend our application to provide the additional information as requested.

The Patent/Exclusivity Statement (Section III) was revised to include the new exclusivity date of June 11, 1999 for Zeneca's new product. Page 13 from the *Approved Drug Products with Therapeutic Equivalence Evaluations, 17th Edition*, Supplement 1, January 1997, which lists the new exclusivity date is also included.

Section III of the ANDA which was revised is being provided in its entirety. To facilitate your review, text changes have been redlined. All other pages within the section remain identical to the original ANDA submission.

RECEIVED
MAY 21 1997
GENERIC DRUGS

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0695
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Bracknell Beeches, Old Bracknell Lane, Bracknell, Berkshire RG127BW
44-344-308803 ■ FAX 44-344-360515

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting Ms. Rosalie A. Lowe, Associate Director, Regulatory Affairs, at (714) 457-2808, or myself at (714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

S:\PRO75102\AMENDS\AMEND1.WPD
Enclosure

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

ANDA 75-102

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan
19 Hughes
Irvine, CA 92618

MAY

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Propofol Injectable Emulsion 1%, (10 mg/mL), in 20 mL syringe

DATE OF APPLICATION: March 31, 1997

DATE OF RECEIPT: April 1, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please amend your application with a revised patent certification and exclusivity statement using the most current version of the Approved Drug Products with Therapeutic Equivalence Evaluations and supplement.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/ 5/6/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GENSIA
LABORATORIES, LTD.

March 31, 1997

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GENERIC DRUGS

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room, Room 150
7500 Standish Place,
Rockville, MD 20855-2773

RE: Propofol Injectable Emulsion (with 0.005% EDTA), 10 mg/mL Prefilled Syringe
ANDA: Number to be Assigned

Dear Mr. Sporn:

Reference is made to a telephone conversation on December 19, 1996 between Ms. Cecilia Parise, Consumer Safety Officer, Office of Generic Drugs and myself regarding the safety issues related to the formulation of Propofol Injectable Emulsion. Ms. Parise indicated that the Agency would only accept ANDA applications for Propofol Injectable Emulsion which contain n the formulation. Therefore, pursuant to Ms. Parise's instructions and in accordance with Section 314.96(a)(1) of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Propofol Injectable Emulsion (Prefilled Syringe) containing in the formulation.

Propofol Injectable Emulsion (with , is a parenteral emulsion preparation to be supplied as:

Strength	Drug Content	How Supplied
10 mg/mL	200 mg Propofol Injectable Emulsion/syringe	200 mg in a 20 mL syringe

Propofol Injectable Emulsion, 10 mg/mL , is the generic version of Diprivan® (Propofol Injectable Emulsion) which is currently manufactured by Zeneca, Ltd. Zeneca's drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 16th Edition.* Our drug product has the same

Gensia Laboratories, Ltd. ■ 19 Hughes, Irvine, CA 92718-1902 ■ (714) 455-4700 ■ FAX (714) 855-8210
Gensia Inc. ■ 9360 Towne Center Drive, San Diego, CA 92121 ■ (619) 546-8300 ■ FAX (619) 453-0095
Gensia Europe, Ltd. ■ Genaresa House ■ 1 Bracknell Beeches, Old Bracknell Lane, Bracknell, Berkshire RG127BW
44-344-308803 ■ FAX 44-344-360515

active and inactive ingredients, dosage form, strength, route of administration, and conditions of use as Zeneca's listed drug product containing

Gensia's manufacturing processes used for Propofol Injectable Emulsion supplied in a prefilled syringe are equivalent to the processes used for Gensia's product supplied in vials for the processes described in the sections listed below. Therefore, reference is made to our amendment ANDA 74-816, which was submitted December 24, 1996 with respect to these sections.

Section VI	Bioavailability/Bioequivalence
Section VII	Components and Composition Statements *
Section VIII	Raw Material Controls
Section IX	Description of Manufacturing Facility
Section X	Outside Firms Including Contract Testing Laboratories
Section XIII	Packaging and Labeling Procedures
Section XVI	Analytical Methods **
Section XVIII	Control Numbers
Section XIX	Sample Availability and Identification
Section XX	Environmental Impact Statement
Section XXI	Other

* Except as this section relates to the container
** Except for the specific lots of finished product

The table below identifies the variation from the vial amendment of ANDA 74-816 which were changed or included to differentiate the prefilled syringe product. These differences include changes to the basis for ANDA, patent certification, labeling, chemistry, manufacturing, control changes, container/closure, and stability. Documentation supporting this information are provided in the sections listed:

Section	Variations from ANDA 74-816 Amendment	Supporting Documentation
II	A summary of the supporting stability lot.	Tables summarizing the information. Reference to **Section XI** for the stability lot.
III	Patent certification and exclusivity statements submitted to reflect current status of the innovator's product.	Orange Book reference.

Section	Variations from ANDA 74-816 Amendment	Supporting Documentation
IV	Comparison between Gensia's versus Zeneca's products for propofol ormulations supplied in a prefilled syringe.	Table summarizing the comparison between Gensia's and the innovator's formulations supplied in a prefilled syringe.
	Comparison between Gensia's versus Zeneca's labeling for both propofo lations supplied in a prefilled syringe.	Side-by-side comparison of Gensia's versus Zeneca's labeling for both propofol EDTA formulations supplied in a prefilled syringe.
V	Labeling for Gensia's Propofol Injectable Emulsion	Draft labeling.
VII	Components and composition statements to reflect the 20 mL prefilled syringe container.	Components and composition statements, and tables for Propofol Injectable Emulsion (with
XI 1.	Summary for manufacturing and processing which reflect the filling of Propofol Injectable Emulsion (with in a prefilled syringe.	The compounding procedure and manufacturing flow diagram for Propofol Injectable Emulsion
	Sterility assurance of the product references volume 4.	Specific sterility assurance information for the manufacture of Propofol Injectable Emulsion plied in prefilled syringe.
2.	Blank batch records which specific for the prefilled syringe product.	Blank batch records for the 20 mL prefilled syringe.
XII	One stability lot to support the prefilled syringe product.	Copies of the executed batch records for the stability lot of Propofol Injectable Emulsion): Lot No. XP6C319F2.
	Finished Product Sampling Plans specific to the prefilled syringe product.	**Finished Product Sampling Plan** for Propofol Injectable Emulsion (with

Section	Variations from ANDA 74-816 Amendment	Supporting Documentation
XV	**Finished Product Specifications and Data Sheet** specific to the prefilled syringe product.	Blank current **Finished Product Specifications and Data Sheet.**
	Stability lot of the prefilled syringe product.	**Finished Product Specifications and Data Sheet** for the stability lot.
XVI	**Finished Product Specifications and Data Sheet** specific to the prefilled syringe product.	Blank current **Finished Product Specifications and Data Sheet.**
	Stability lot of the prefilled syringe product.	**Finished Product Specifications and Data Sheet** for the stability lot.
XVII	One stability lot of the 20 mL prefilled syringe was manufactured and stability data is presented. In addition, the 20 mL vial lot (Lot No. XP6N319), which is the subject of ANDA 74-816, is presented in support of the stability section of this application.	Stability Report

Four copies of the proposed labeling have also been provided in **Section V** of the application in both the archival and review copies.

The application consists of four (4) volumes and has been formatted in accordance with the Office of Generic Drug's Policy and Procedure Guide #30-91 issued April 10, 1991; and, as modified by FDA's October 14, 1994 letter to all NDA, ANDA, and AADA applicants. Copies are provided as follows:

1) One (1) Archival Copy bound in Blue Jackets
2) One (1) Review Copy bound in Red Jackets

A true copy of this application, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration of Irvine, California, Los Angeles District Office.

Since the product which is the subject of this application is non-compendial, three (3) additional methods validation packages have been included and are marked "Analytical Methods." These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting Ms. Rosalie A. Lowe, Associate Director, Regulatory Affairs, at (714) 457-2808, or myself at (714) 455-4709, or by facsimile at (714) 583-7351.

Sincerely,

Donald J. Harrigan

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

cc: Ms. Elaine Messa
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Boulevard, Suite 300
Irvine, CA 92715

Field Copy Certification

Gensia Laboratories, Ltd., certifies that a true copy of our application for Propofol Injectable Emulsion), 10 mg/mL, Prefilled Syringe, which was submitted to the Agency on March 31, 1997, was also provided to the Irvine, California, Los Angeles District Office of the U.S. Food and Drug Administration.

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

3/31/97
Date

Debarment Certification

As required by the Generic Drug Enforcement Act of 1992, Gensia Laboratories, Ltd., certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Act, in connection with our application for Propofol Injectable Emulsion (with 0.005% EDTA), 10 mg/mL, Prefilled Syringe.

We are unaware of any convictions of crimes (as specified in section 306 (a) and (b) of the Act) within the previous five years of any Gensia employees or affiliated company, or employees of the affiliated companies responsible for the development or submission of this abbreviated application for Propofol Injectable Emulsion (with 0.005% EDTA), 10 mg/mL, Prefilled Syringe.

Donald J. Harrigan, R.Ph.
Director, Regulatory Affairs

3/31/97
Date