CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

TITLE: PROPOFOL INJECTION EXCLUSIVITY DECISION

DATE: MARCH 17, 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date • March 17, 1997

From Director, Center for Drug Evaluation and Research

Subject Exclusivity Decision on Propofol Injectable Emulsion

To Director, Office of Generic Drugs
Deputy Director, Office of Generic Drugs
Director, Office of Pharmaceutical Science
Director, Office of Drug Evaluation III
Associate Director for Medical Policy

This memorandum is in response to the Office of Generic Drugs' (OGD) January 28, 1997 document entitled "Propofol Injectable Emulsion: Exclusivity Summary" and Dr. Botstein's February 11, 1997 memo entitled "Exclusivity for Propofol with EDTA." My decision on this matter and the reasons for the decision are set forth here.

I have carefully read the above documents and their attachments, as well as a February 24, 1997 memo from Dr. Temple entitled "Propofol Injectable Emulsion: Exclusivity," a February 12, 1997 document submitted by on behalf of and containing an evaluation by a letter from Zeneca Pharmaceuticals Group to Robert Bedford, M.D. dated July 29, 1994, and relevant portions of the administrative record of NDA 19-627, including portions of the transcript of the June 10, 1994 meeting of the Anesthetic and Life Support Drugs Advisory Committee. I have concluded that the sponsor, Zeneca Pharmaceuticals, has met the requirements under the FD&C Act for obtaining exclusivity of a drug product that is the subject of a supplement to an approved application [Sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv)]. I have determined that the three conditions set forth in the Act have been met: (1) the supplement contained reports of new clinical investigations; (2) these new clinical investigations were essential to approval of the supplement; and (3) the investigations were conducted by the applicant.

The differences of opinion about the exclusivity opinion arose because of disagreements over points (1) and (2). It has not been disputed that the sponsor conducted the studies.

New Clinical Investigations

In order to qualify as "clinical investigations" under the regulations [21 CFR 314.108(b)(5)], the new clinical investigations must not be bioavailability investigations. Clearly, the studies at issue were intended to evaluate outcomes other than, or in addition to, the rate and extent of absorption of propofol and, thus, were not bioavailability investigations. This point is agreed upon by OGD and ODE III reviewers. For a clinical investigation to be "new", the regulations require that it be "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied upon by the Agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." OGD has concluded that the investigations contained in Supplement 0-27 do not qualify as "new" under the above definition for reasons outlined in the OGD memo of January 28, 1997. However, I find that OGD has not interpreted this language correctly. To be "new" clinical investigations, the results of the investigations cannot have been relied upon by FDA for demonstrating efficacy or safety of a previously approved drug product, nor can they duplicate the results of relied upon investigations. The studies in question literally were "new" (i.e., newly performed) and have not been previously relied upon by FDA, nor do they duplicate previous results. Therefore, they are new clinical investigations.

OGD has also raised the issue that the clinical investigations in Supplement 0-27 could be considered "limited confirmatory safety studies," although the Agency has not defined this phrase more specifically. The size and extent of the clinical studies that were performed are not consistent with the term "limited confirmatory safety studies." The OGD suggestion may reflect the belief that the Agency COULD have requested merely "limited confirmatory safety studies;" however, the fact remains that the Agency did not do this.

Essential to Approval

The issue of whether these studies were "essential to approval" is raised in the review and obliquely by the OGD comments on "limited confirmatory safety studies." It is clear from the administrative record that both the reviewing new drug division and the members of the Anesthetic and Life Support Drugs Advisory Committee considered the performance of these clinical studies essential to the demonstration of safety and efficacy of the new formulation of propofol. points out that, subsequently, Dr. I. L. Tyler, in his January 5, 1996 medical officer review of

the completed studies in the NDA supplement, asserts that the concerns about EDTA effects on calcium and magnesium could have been assuaged by calculations of the maximum chelating effect on these ions, and also by a review of the experience with Calcium Disodium Versenate. Additionally, Dr. Tyler asserts that concerns about the renal toxicity of the new formulation could have been better addressed by close monitoring of urinary sediment results. With regard to the first point, I note that the Advisory Committee members were sufficiently concerned about calcium and magnesium effects that they discussed the advisability of conducting animal safety studies before doing human trials. While Dr. Tyler's calculations are reassuring with respect to potential large shifts in ionized calcium and magnesium, such calculations may not take into account all the factors in an in vivo system, which is why clinical safety studies are often required to address this type of safety concern. With regard to Dr. Tyler's second point, it is likely the case that urinary sediment examinations could have detected early evidence of renal tubular damage. However, the fact remains that the safety studies, as conducted, did not reveal an excess occurrence of renal insufficiency in patients treated with the test agent, and this provided evidence of safety for the kidney.

The fact that the studies of the new formulation, once performed, provided considerable reassurance about the safety of the formulation, does not render them nonessential.

Finally, I note that the letter from alleges that Zeneca was including EDTA in Diprivan as far back as 1992, well prior to FDA approval of the change in formulation. supports his assertion with data from two laboratories, each of which detected EDTA in Diprivan samples acquired from Zeneca prior to approval of the supplement to add EDTA. Analyses conducted at FDA laboratory facilities have not confirmed the presence of EDTA in propofol manufactured prior to approval of the supplement. Should the Agency obtain additional evidence of the presence of EDTA in Zeneca's propofol product prior to the time FDA approved the addition of this ingredient, the Agency will take whatever action is appropriate.

Summary

I find that the sponsor, Zeneca Pharmaceuticals, is entitled to three years of exclusivity as set forth in the Act and regulations.

Janet Woodcock, M.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

January 28, 1997

From: **Deputy Director**
Office of Generic Drugs

Through: **Director**
Office of Generic Drugs

Through: **Director**
Office of Pharmaceutical Science

To: **Director**
Center for Drug Evaluation and Research

Re: **Propofol Injectable Emulsion: Exclusivity Summary**

Attached to this memorandum is an Exclusivity Summary that the Office of Generic Drugs (OGD) has prepared in the matter of exclusivity for Zeneca's Propofol Injectable Emulsion (Diprivan). This summary pertains to the applicant's Supplement-027 to NDA 19-627. This supplement requested approval to add EDTA 0.005% to the drug product to retard bacterial growth during clinical use. In an Exclusivity Summary dated June 11, 1996, the review division responsible for this NDA, the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), recommends that a positive determination for exclusivity be made for Supplement-027. According to 21 CFR 5.93, the determination of exclusivity resides with the Office of Generic Drugs. Recognizing that this determination has important implications beyond this Supplement-027 and also because the OGD recommendation is not the same as that recommended by HFD-170, the OGD is forwarding its conclusion to you for concurrence.

Attachments

cc: Murray Lumpkin, M.D.
Robert Temple, M.D.
Paula Botstein, M.D.
Curtis Wright, M.D.
Elizabeth Dickinson

EXCLUSIVITY SUMMARY

NDA 19-627
DIPRIVAN INJECTABLE EMULSION
Zeneca Pharmaceuticals

I. Background

In the early 1990's, cases of sepsis were reported in patients receiving Propofol Injectable Emulsion. The FDA, CDC, and the applicant, Zeneca Pharmaceuticals, determined that this clinical problem arose because of inappropriate aseptic technique utilized by practitioners handling the product, coupled with a propensity of the drug product to promote bacterial growth once contamination had occurred.

As a result of the contamination problem, the applicant distributed "Dear Colleague" letters in July, 1990, and February, 1991, advising practitioners of the problem and describing proper handling of the drug product. The number of reports decreased, but in 1993 another cluster of contamination cases was reported. A series of meetings that included FDA, CDC, and the applicant were held, during which the applicant reported that EDTA reduced bacterial growth in propofol.

In June 10, 1994, a closed session of the Anesthesia Advisory Committee was held to discuss the implications of adding EDTA to the formulation of Propofol Injectable Emulsion. The Anesthesia Advisory Committee accepted the Zeneca proposal to add EDTA to the propofol drug product. The Advisory Committee also recommended that clinical studies be conducted to assess the risk of adding EDTA, given that high volumes of Propofol Injectable Emulsion may be administered in certain clinical settings. This recommendation was accepted by HFD-170.

To meet the recommendations of HFD-170 and the Anesthesia Advisory Committee, Zeneca performed and submitted the results of five clinical studies that compared Propofol Injectable Emulsion with EDTA (Diprivan/EDTA) to Propofol Injectable Emulsion without EDTA (Diprivan). The results of these five clinical studies were submitted in Supplement-027 to NDA 19-627 on December 29, 1995. The HFD-170 medical officer's review of the five studies appears in Attachment A. On June 11, 1996, HFD-170 approved Supplement-027 for the new formulation utilizing EDTA. On that date, HFD-170 also forwarded to DDIR an Exclusivity Summary,

recommending that three years exclusivity be granted to Diprivan\EDTA (Attachment B). Medical officers from OGD and HFD-170 provided an overview of the five clinical trials that appears in Attachment C. In addition, the Director, HFD-170, provided a commentary on the decision to provide exclusivity to Zeneca for the five clinical studies performed with Diprivan/EDTA. This commentary appears in Attachment D.

II. Discussion

A. Stipulations of the Type of Studies Supportive of a Determination of Exclusivity

The regulations describing the requirements for exclusivity are found in 21 CFR 314.108(b)(5), which state that exclusivity will be granted for a change which represents a therapeutic advance if new clinical investigations, which are not bioavailability investigations, were performed or sponsored by the applicant in support of the change, providing that the studies were required by the FDA. The words delineating these stipulations of 21 CFR 314.108 are reproduced below:

Requirement 1:

> Clinical investigations - any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Requirement 2:

> Essential to approval - with regard to an investigation, there are no other data available that could support approval of the application.

Requirement 3:

> New clinical investigations - an investigation in humans that the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product and do not duplicate the results of another investigation that was relied on by the agency to demonstrate effectiveness or safety in a new patient population of a previously approved drug product...

Requirement 4:

Conducted by or sponsored by the applicant.

All four requirements must be met to support a determination of exclusivity. Regarding these four stipulations of 21 CFR 314.108, the OGD has reached the following conclusions:

1. 21 CFR 320.25 states that bioavailability measures the rate and extent of absorption of the active moiety. The primary objective of the five Zeneca studies, as determined by the analysis in Attachment C, was not, however, to assess the rate and extent of absorption of propofol but rather to assess the impact of Diprivan/EDTA on the mineral homeostasis in comparison to Diprivan without EDTA.

   The Director, HFD-170, has also noted that the efficacy endpoints were included in the five Zeneca studies, and OGD agrees with this point (Attachment D). However, OGD believes that where the focus of the five Zeneca studies turns to either safety or efficacy of propofol itself the studies should then be regarded as bioavailabililty (bioequivalence) studies. OGD notes that bioavailability (bioequivalence) studies with clinical endpoints may be used to document unchanged safety and efficacy of the active moiety, as stipulated in 21 CFR 314.24(b)(4).

   > *Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product, for purposes of establishing bioequivalence, or appropriately designed comparative clinical trials for purposes of demonstrating bioequivalence.*

   Based on this analysis, the OGD concludes that the five Zeneca studies were not bioavailability studies for the safety endpoints focusing on mineral homeostasis. Where these studies focus on the effect of EDTA on the safety or efficacy of propofol, OGD concludes that they are bioavailability (bioequivalence) studies according to 21 CFR 314.24

2. OGD notes that Anesthesia Advisory Committee recommended that studies of the type executive by Zeneca be performed and

that HFD-170 endorsed these recommendations.

Based on this information, the Office of Generic Drugs concludes that the stipulation of 21 CFR 314.108 in Requirement 2 are met.

3. 21 CFR 314.108 states that to qualify for exclusivity, the clinical studies must be new. According to 21 CFR 314.108:

New clinical investigations means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product...

The five clinical studies performed by Zeneca did not demonstrate substantial evidence of effectiveness of propofol for any indication. OGD notes that the Indications section of the labeling for Diprivan/EDTA did not change as a result of the five Zeneca studies. In addition, OGD believes that the five Zeneca studies did not provide information about the safety of Diprivan/EDTA in a new patient population. OGD again notes that the patient populations for whom Diprivan/EDTA is indicated did not change in the approved product labeling based on the information gained from the five Zeneca studies.

Based on this analysis, OGD concludes that the stipulations of 324.108 for new clinical investigations were not met.

4. The five Zeneca studies were conducted by or performed by Zeneca.

Because Zeneca sponsored the five clinical trials, the Office of Generic Drugs concludes that the stipulations of 21 CFR 314.108 for Requirement 4 were met.

B. Allowance for Limited Confirmatory Safety Studies

In addition to the primary determination noted in A above, OGD believes that the studies performed by the applicant could also be

considered 'limited confirmatory testing.' Limited confirmatory testing for safety is allowed according to the preamble to the proposed rule [see 54 FR 28880; July 10, 1989, relative to 505(j)(2)(C) petitions]. According to this preamble:

If preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an abbreviated new drug application is not appropriate for the proposed drug product, and FDA will not approved a petition. However, under certain circumstances, data from limited confirmatory testing to show that the characteristics that make the proposed drug product different from the listed drug do not alter its safety and effectiveness may be accepted in a petition or as additional data to be included in an ANDA resulting from an approved petition.

Continuing, the preamble states that by limited confirmatory testing, FDA means simple studies intended to rule out unlikely problems. Such tests do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective. The concept of limited confirmatory testing has also been allowed for certain ANDA's so long as the clinical or animal testing done was used to support the generic drug product rather that the underlying safety and effectiveness of the reference listed drug.

In the past, the FDA has never attempted to develop criteria to defined what level of studies are necessary to be considered beyond 'limited confirmatory studies.' Because the studies performed by Zeneca were not safety studies designed to assess the safety of propofol itself, but were rather studies assessing the impact of an inactive ingredient that did not relate to propofol's safety, OGD concludes that the studies performed by Zeneca could be interpreted as limited confirmatory studies.

C. CONCLUSION

Because of the analyses in A/1 and A/3, and also because the clinical studies conducted by Zeneca could be considered primary safety studies, specifically limited confirmatory safety studies, OGD recommends that three years of exclusivity should be denied Zeneca for Diprivan/EDTA.

ATTACHMENT A

HFD-170 Medical Officer's Review of five clinical studies

ATTACHMENT B

HFD-170 Exclusivity Summary recommending three years exclusivity

ATTACHMENT C

OGD/HFD-170 Medical officers overview of the five clinical studies

ATTACHMENT D

Director, HFD-170, opinion in the matter of exclusivity for Diprivan/EDTA.

NDA#: 19-627
Generic name and form: Propofol with 0.005% EDTA
Route of Administration: IV
Sponsor: Zeneca Pharmaceuticals
Letter Date: 12/22/95
Date Completed: 1/5/96

MEDICAL OFFICER REVIEW
NDA REPORT
Propofol with 0.005% EDTA
IV

"ZD0859#1"

Type of Submission: NDA REPORT
Date Received: 1/2/96
Reviewer: I. L. Tyler, Ph.D., M.D.
Peer Reviewer: Robert Bedford, M.D.

Abstract

Diprivan is Zeneca Pharmaceuticals' trade name for propofol, a sedative hypnotic agent dissolved in Intralipid. Since the introduction of Diprivan in 1989, the FDA has been concerned regarding ongoing reports linking bacterial contamination of Diprivan to postoperative sepsis. In response, Zeneca examined numerous bacteriostatic agents, finally determining that the addition of 0.005% disodium EDTA — a metal chelating agent — to Diprivan would accomplish their goal of reducing the multiplication of bacterial contaminants to less than a factor of 10 per 24 hours; the Phase III development program for this product was reviewed and approved by the Anesthetic and Life Support Drug Advisory Committee on June 5, 1994. This new formulation is designated ZD0859#1.

Zeneca identified Ca^{++} and Mg^{++} homeostasis and renal damage as possible risks associated with ZD0859#1 and elected to examine Ca^{++}, Mg^{++}, BUN, and creatinine plasma levels during infusions of ZD0859#1 to determine the extent of these risks.

In fact, simple upper-bound calculations (Appendix A) demonstrate that neither Ca^{++} nor Mg^{++} depletion are risks with ZD0859#1. By contrast, Zn^{++} homeostasis during prolonged ICU use is a real concern. Furthermore, Calcium Disodium Versenate (CDV) — an FDA-approved antidote for lead poisoning — is Ca^{++}-saturated Disodium EDTA. (Ca^{++}-saturation does not affect EDTA's Zn^{++} chelating potential — Appendix B). Zinc depletion as well as the risk of renal damage figure prominently in the package insert for CDV.

Approval, with appropriate Phase IV studies, is recommended *provided that modifications in the proposed package insert reflect ZD0859#1's similarities to CDV and adequately stress appropriate risk management.*

1 Material Reviewed

Volumes: 1, 41.1, 68.2, 68.15, 68.16, 68.18, 68.19, 68.22, 68.23, 68.27, 68.29, 68.31, 68.33-68.37 .

2 Animal Pharmacology/ Toxicology

A single study was performed. It evaluated the effects on beagles of ZD0859#1 and of ZD0859#1 containing 10 times the normal concentration of EDTA. Doses were sufficient to maintain maximal anesthesia over five four-hour periods. Three to four days were allowed for recovery between each of the five infusions. Increased levels of hemosiderin in Kupffer cells were found in 80% of livers of both groups. These levels had returned to normal by the end of the observation period. No increases were seen in the control group.

The sponsor hypothesizes that the hemosiderin elevation was consistent with a hemolysis due to the "large volumes of fluids" delivered. If the study had been designed differently — if the control group had received identical treatment but without the added EDTA — this hypothesis could have been corroborated by the presence of identical deposits in the controls. Unfortunately, the controls received no treatment and no hemosiderin deposits occurred in their livers. Furthermore, the volume of fluid given to the EDTA groups (3 ml/kg/hr, only 85% of which is in the form of distilled water) was not large. Infusing this volume in the beagle is equivalent to an adult human drinking six ounces of water per hour for four hours. In addition, renal hemosiderosis — the usual complication of intravascular hemolysis — was not seen. Another possibility is that serum Fe^{++} was chelated by EDTA rather than attaching to hemosiderin and was deposited in the liver following hepatic metabolism of EDTA. (In humans, however, most EDTA is excreted unchanged by the kidneys rather than being metabolized.)

3 Clinical Background

3.1 Introduction

EDTA chelates di- and trivalent metal ions and has a long history of safe, FDA-approved use as a preservative in both foods and pharmaceuticals because of its ability to chelate Ca^{++} — a necessary intermediary in numerous microbial metabolic/mitotic reactions. In addition, EDTA was previously added to stored blood as an anticoagulant because free Ca^{++} is required in the coagulation cascade. Calcium disodium edetate — Ca^{++}-saturated disodium EDTA— is approved for IM/IV use and is marketed as Calcium Disodium Versenate (CDV). Zinc depletion — but not hypomagnesemia — is mentioned as a side effect of this compound.

The recommended dosing for CDV is two hundred times the maximum anticipated for ZD0859#1. For ions such as Mg^{++}, where plasma concentrations are relatively high, this dose ratio is significant — if Mg^{++} depletion is not a risk associated with CDV use, it won't be a risk associated with ZD0859#1 use. In contrast, for trace metal ions such as Zn^{++} and Co^{++}, exposure time — rather than total dose — is most important. This is because the dose-response for trace metal depletion by EDTA saturates at a very low dose. At an infusion rate well below the recommended infusion rate, CDV would already have chelated *all* of the minute pool of the trace metal ion in the plasma as well as all trace metal diffusing into the plasma from body stores. Increasing the CDV infusion rate beyond this critical value would have no further effect on trace metal depletion. It will be shown later that this saturation occurs at doses even lower that those expected during normal ICU infusions of ZD0859#1. Zeneca identified renal damage and Ca^{++} and Mg^{++} homeostasis as possible risks associated with the EDTA in ZD0859#1 and elected to follow Ca^{++}, Mg^{++}, BUN, and creatinine plasma levels during infusions of ZD0859#1 to determine the extent of these risks.

Rising BUN and creatinine plasma levels are late signs of renal damage. Urinalysis is the best guide to early renal pathology and would have been more appropriate choices for following the effects of EDTA on the kidney.

In addition to the lack of evidence for Mg^{++} depletion following CDV use, the chelating properties of disodium EDTA together with some simple calculations based on expected maximum dosing rates of ZD0859#1 suggest that Zeneca's concerns regarding Ca^{++} and Mg^{++} depletion were not well-founded. The relevant calculations are presented in detail in Appendix A. They demonstrate:

> In order to reduce the ionized fraction of magnesium by 10% in a 70 kg patient, a bolus of at least 2.5 L of ZD0859#1 would be required. In contrast, the maximum clinically acceptable bolus dose of ZD0859#1 is 40 ml — less than 2% of 2.5 L. In order to reduce the ionized fraction of calcium by 10% in a 70 kg patient, a bolus of at least 7 L of ZD0859#1 would be required.
>
> Losses of calcium and magnesium due to chelation during long-term ICU infusion therapy with ZD0859#1 are of even less concern. Even if EDTA chelated only Ca^{++} or only Mg^{++} the modest resultant daily losses of Ca^{++} and Mg^{++} would be replenished by the relatively massive bone stores of calcium and intracellular stores of magnesium. Intracellular Mg^{++} stores could be expected to drop only 10% after 19 days of the maximum recommended ICU ZD0859#1 infusion rate. The percent loss of total body Ca^{++} would be minimal after 19 days.

3.2 Relevant Human Experience

In Appendices A and B it is shown that, with the exception of effects on Ca^{++} homeostasis, the EDTA in ZD0859#1 is equivalent to CDV. Therefore, the relevant human experience with EDTA is that for CDV.

Of course, doses of EDTA from ZD0859#1 would be expected to be considerably lower than those used in the CDV treatment of plumbism. In some cases, for example renal toxicity, the risks for ZD0859#1 could reasonably be expected to be proportionately lower. In others — most notably Zn^{++} depletion potential — the dose-response could be expected to have saturated well below the recommended CDV infusion rates. In these latter situations, total infusion time, rather than total dose is likely to be a more relevant consideration.

The following points are taken directly from the corresponding headings in the package insert[1] for CDV *with Reviewer comments added in italics*. Each should be considered as a possible addition to the labeling for ZD0859#1.

Concurrent plumbism may have contributed to some of the adverse events listed for CDV. Those which are definitely associated with lead poisoning are followed by an asterisk (*).

CALCIUM DISODIUM VERSENATE

(Excerpts from the Package Insert)

CLINICAL PHARMACOLOGY:

1. EDTA is poorly absorbed from the GI tract.

   This fact is important because most human exposure to EDTA has been as a food additive. Furthermore, most animal studies involved PO administration of EDTA. This is not always made clear in abstracts.

[1] Physician's Desk Reference. 49th Edition. Medical Economics Data Production Co., Montvale NJ, 1995, pp 1380-1381.

4. The urinary excretion of zinc is considerably increased following parenteral EDTA administration.[2]

In the plasma, 6-8% of Zn^{++} exists as free ion, 1/3 is attached loosely to albumin and the remainder is bound tightly to globulins[3]*. No data are available regarding the ability of EDTA to extract Zn^{++} from globulins. There is some evidence that globulin-bound Zn^{++} does not freely exchange with the other pools.*[3] *This implies that the dose dependence of Zn^{++} depletion may saturate at relatively low CDV infusion rates.*

CONTRAINDICATIONS:

1. EDTA should not be given during periods of anuria, nor to patients with active renal disease or hepatitis.

Incipient renal failure is endemic to the ICU.

PRECAUTIONS:

General Precautions:

1. In high doses, EDTA is toxic to the renal tubules. Nephrotoxicity is dose-dependent and may be reduced by assuring adequate diuresis before therapy begins. Urine flow must be monitored throughout therapy and treatment must be stopped if severe oligurea develops. Proximal tubule hydropic degeneration usually recovers upon cessation of therapy.

Laboratory Tests:

1. Urinalysis and urine sediment, renal and hepatic function and serum electrolyte levels should be checked before each course of therapy and then be monitored daily during therapy in severe cases, and in less serious cases after the second and fifth day of therapy. Therapy must be discontinued at the first sign of renal toxicity.

2. The presence of large renal epithelial cells or increasing number of red blood cells in urinary sediment or greater protienuria call for immediate stopping of EDTA administration.

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[2] Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium EDTA treatment of lead-poisoned children. J Pharmacol Exp Therapeu 1986; 239, 829-835.

[3] Fairweather-Tait S et al. The measurement of exchangeable pools of zinc using the stable isotope ^{70}Zn. Brit J Nutrit 1993; 70, 221-34.

The implication is that examination of urinary sediment would be critical for the early detection of ZD0859#1-induced renal damage.

3. Alkaline phosphatase values are frequently depressed (possibly due to decreased serum zinc levels), but return to normal within 48 hours after cessation of therapy.

Drug Interactions:

1. There is no known drug interference with standard clinical laboratory tests.

When blood samples are inappropriately stored in EDTA-containing test tubes prior to platelet analysis, platelet clumping results. Platelet clumping in vivo due to an EDTA infusion could precipitate ischemic events. It is encouraging to see that the low plasma EDTA concentrations resulting from CDV infusions (at 200 times the expected EDTA infusion rate for ZD0859#1) are not associated with this phenomenon.

2. Steroids enhance the renal toxicity of EDTA in animals.[4]

Steroids figure prominently in the therapy of many ICU patients. In particular, steroids are used in severe asthmatics. Propofol/ZD0859#1 sedation is being promoted as an alternative to muscle relaxants in ventilator-dependent asthmatics because asthmatics seem to exhibit a greater susceptibility to the syndrome of prolonged (weeks to months) paralysis following ICU muscle relaxant use.

3. EDTA interferes with the action of zinc insulin preparations by chelating the zinc.[4]

Most longer-acting insulin preparations, including the frequently-used Lente insulin are zinc suspensions. The purpose of the Zn^{++} is to precipitate the formation of amorphous insulin. This form does not diffuse out of the subcutaneous tissue as rapidly as the crystalline form. Theoretically the EDTA in ZD0859#1 could diffuse into the intersititial space and convert longer-acting insulin to regular insulin thereby precipitating hypoglycemia.

[4] Drug Evaluations, 6th Edition, American Medical Association, Saunders, Philadelphia, 1986, pp. 1637-1639.

However, long-acting insulin preparations are used infrequently in the CR and ICU.

Pregnancy:

1. Studies in rats at doses up to 13 times the human dose revealed no evidence of impaired fertility or harm to the fetus.[5]

This was, however, a single dose given by oral intubation.

2. Another study in rats at doses up to about 25 to 40 times the human dose revealed evidence of fetal malformations which were prevented by simultaneous supplementation of dietary zinc, 1000 ppm.[6]

Again, the EDTA was per orum. Apparently there is some absorption. No data are available on how much, though, so until proven otherwise ZD0859# 1 should be considered capable of causing fetal malformations in rats. The teratogenic potential of EDTA is probably related to its effect on Zn^{++} homeostasis because the developing fetus is extremely sensitive to zinc depletion.

ADVERSE REACTIONS

Cardiovascular:

The submitted studies adequately rule out the importance of these effects at the low dosing rates expected in ZD0859# 1.

1. Hypotension.

2. Cardiac rhythm irregularities

Renal:

1. Acute necrosis of proximal tubules which may result in fatal nephrosis.

2. Infrequent changes in distal tubules and glomeruli.

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[5] Schardein JL, et al. Teratogenesis studies with EDTA and its salts in rats. Toxicol Appl Pharmacol 1981; 61:423-8.

[6] Swenerton H, Hurley LS. Teratogenic effects of a chelating agent and their prevention by zinc. Science 1971; 173:62-4.

Urinary:

1. glycosuria*, protienuria

2. microscopic hematuria and large epithelial cells in urinary sediment.

Hepatic:

1. Mild increases in SGOT and SGPT are common and return to normal within 48 hours after cessation of therapy.

Immunogenic:

1. Histamine-like reactions (sneezing, nasal congestion, lacrimation), rash.

Hematopoetic:

1. Transient bone marrow depression*, anemia.*

Metabolic:

1. Zinc deficiency.

Cumulative losses of Zn^{++} in urine correlate negatively with body mass.[2] This suggests that the pediatric population is at a higher risk for Zn^{++} loss.

3.3 Foreign Experience

ZD0859#1 has not been marketed in a foreign country.

3.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

The pharmacokinetics of ZD0859#1 was investigated in healthy volunteers (Trial 1) and in pediatric patients (Trial 3). These studies are summarized under Description of Clinical Data Sources below. The added EDTA did not significantly affect the pharmacokinetics of propofol in either trial.

The pharmacokinetics of EDTA are as follows:[1]

In blood, all the EDTA is found in the plasma. It does not appear to penetrate cells. It is distributed primarily in the extracellular fluid with only about 5% of the plasma concentration found in the spinal fluid.

The half-life of EDTA is 20 to 60 minutes. It is excreted primarily by the kidney, with about 50% excreted in one hour and over 95% within 24 hours.[7] Almost none of the compound is metabolized.

3.5 Directions for Use

Directions submitted by the sponsor regarding dosage and administration of ZD0859#1 are identical to those for Diprivan.

> *Specifically, there is no recommendation similar to CDV's that infusions of ZD0859#1 be discontinued after 5 days to allow repletion of Zn^{++} stores.*

The warning regarding microbial contamination differs from that for Diprivan only in that the addition of EDTA "to retard the rate of growth" is documented together with the caveat that "Diprivan can still support the growth of microorganisms as it is not an antimicrobially preserved product under USP standards".

> *This conforms to the following Consultation Conclusion of the FDA microbiology group: "The addition of preservative to the concentration in this product does not provide adequate levels of preservation to conform to the USP <51> definition of Antimicrobial Preservative Effectiveness. However, the added preservative does provide a higher level of protection against the proliferation of contaminating organisms introduced during handling as compared to the original product formulation. Product labeling should not state or imply that the reformulated product is preserved and further, should emphasize the requirement of the use of strict aseptic technique in the handling of this product."*

4 Description of Clinical Data Sources

All studies were performed in the U.S. after FDA approval of protocols.

5 Results

All trials were randomized and double-blind.

Trial 1: A Comparison of the Safety, Efficacy, and Pharmacokinetics of ZD0859#1 with that of Diprivan in Healthy Subjects.

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[7] The pharmacological basis of therapeutics, 7th Edition, Edited by Goodman and Gilman. Macmillan Publishing Company, New York, 1985, pp. 1619-1622.

Ninety-nine healthy volunteers received bolus doses of 2 mg/kg followed 1 hr. later by an hour-long infusion of 25, 50, 100, or 200 μg/kg/min of ZD0859#1 (N=50) or Diprivan (N=49) in a two-period crossover study with a fifteen day wait between the ZD0859#1 and Diprivan arms. The maximum total dose of ZD0859#1 given to any patient was 125 ml — capable of reducing the ionized calcium concentration by less than 0.2% or the serum magnesium concentration by less than 0.6% even if given as a single rapid bolus rather than bolus plus slow infusion. Serum ionized calcium, magnesium, BUN and creatinine levels were determined 1, 2, 4, 8, 16, 30, 60 minutes after the start of the bolus-plus-infusion and again 4, 16, 60, and 120 minutes after discontinuation of the infusion. Parathyroid hormone levels were also measured in some patients.

As expected, there were no significant differences between the effects of ZD0859#1 and propofol on measured plasma calcium and magnesium concentrations. As expected, BUN and creatinine levels did not differ between the two treatments. As expected, there was no difference in the pharmacokinetic and pharmacodynamic properties of the two drugs.

No significant differences were seen in the odds ratio for occurrences of adverse events.

Trial 2: ZD0859#1 vs. Diprivan with High-Dose or Low-Dose Opioid in Cardiac Anesthesia.

One hundred and two elective patients with good cardiac function scheduled for their first open-heart surgery were randomly assigned to one of the four groups. The low-dose opioid + ZD0859#1 group (N=25) received the highest total doses of EDTA. The maximum total amount of ZD0859#1 used on any patient was less than 50 ml — capable of reducing the ionized calcium concentration by less than 0.1% or the serum magnesium concentration by less than 0.3% even if given as a single rapid bolus rather than bolus plus slow infusion. Ionized calcium and magnesium were measured at baseline; 15 min after induction; 15 min. before, 15 and 45 min after initiation of bypass; on arrival in the ICU; and 1 h. after extubation.

A statistically, but not clinically significant difference between the ZD0859#1 and Diprivan groups was seen in the systemic vascular resistance as determined by pulmonary artery cardiac output at a single point — 30 min. after initiation of bypass.

Five patients (10%) in the ZD0859#1 group had hypotensive episodes whereas only 2 (4%) in Diprivan group had them. Four patients (8%) in the ZD0859#1 group had hypertensive episodes whereas only 1 (2%) in the Diprivan group had them. Neither incidence rate is remarkable for open-heart surgery. Hemodynamic instability in the face of normal serum calcium and magnesium levels are not an expected side effect of low doses of EDTA.

Otherwise, no significant differences were seen between the effects of the two formulations.

Trial 3: ZD0859#1 vs. Diprivan for Maintenance in Children.

Thirty-seven children scheduled for non-cardiac surgery lasting at least 30 min. were randomized to receive either ZD0859#1 (N=19) or Diprivan (N=18) at an infusion rate beginning at 200 μg/kg/min together with N_2O for maintenance of anesthesia. The youngest patient was 8 mo. Two other patients were under 2 yr. Twenty-five were between 2 and 12 yr. Three additional open-heart patients between 2 and 12 yr. received ZD0859#1 and were included in the safety analysis.

Plasma calcium and magnesium levels were determined at t=0, 5, 10, 15, and 30 minutes after the start of the infusion and at the time the infusion was turned off. In the non-cardiac group, mean plasma Ca^{++} and Mg^{++} levels remained in the normal range at all times, but four patients (22%) in the ZD0859#1 group and one (6%) in the Diprivan group developed transient, mild hypocalcemia ($1.0 \geq Ca^{++} \geq 0.7$ mmol/L) at t=15 min. There was no concomitant hypomagnesemia. The three ZD0859#1 hypocalcemia patients for which cumulative dose data corrected for body surface area were available had received relatively low doses of ZD0859#1.

Trial 4: ZD0859#1 vs. Diprivan for Sedation in [Seventy-five] Post-surgical ICU [patients requiring at least 2 hr. of post-operative mechanical ventilation].

and

Trial 5: ZD0859#1 vs. Diprivan for Long-Term ICU Sedation [in Fifty-two patients, 18-75 yr., requiring mechanical ventilation for pulmonary dysfunction].

Patients were randomized to receive either ZD0859#1 (N=64) or Diprivan (N=63) as a sedative agent and then to receive either light (responsive to verbal commands) or deep sedation. Propofol infusion rates ranged from 2 to 75 μg/kg/min for times ranging from 3 hr. to 21 d. and total propofol doses ranging from 80 to 150,000 mg (8 to 15,000 ml). Calcium and magnesium serum levels were determined at 1 hr. and 4 hr. on the first day, at 1200 and at 1800 on the second day, and at 1200 on the remaining days of the infusion. Serum BUN and creatinine levels were measured at baseline, 4 hr., and again on day 2.

The maximum infused dose of ZD0859#1 was 4000 ml. A 70 kg patient receiving this much EDTA as a bolus could theoretically experience a transient 10% drop in serum ionized calcium or a 25% drop in ionized magnesium. In fact, at the infusion rates studied, serum re-supply by endogenous stores alone would maintain

homeostasis of serum Ca^{++} and Mg^{++} levels. As expected, no statistically significant differences in changes from baseline for calcium, magnesium, creatinine, or BUN were found in comparing ZD0859#1 with Diprivan.

Because of the study populations, numerous adverse events occurred but they were relatively evenly distributed between the Diprivan and ZD0859#1 groups.

Relevance of All Clinical Trials to Zn^{++} homeostasis:

The risk of Zn^{++} depletion after 5 days of infusion figures prominently in the labeling for CDV. There may be an approximately equal risk of Zn^{++} depletion after 5 days of ICU use of ZD0859#1. This is true in spite of the fact that the dose of EDTA infused after 5 days of ZD0859#1 use is only 1/200 of the EDTA infused after 5 days of EDTA therapy. That is because the dose dependence of Zn^{++} losses due to EDTA can be expected to saturate at infusion rates well below the recommended rates for either CDV or ZD0859#1: The low-normal pool of plasma Zn^{++} readily available for chelation is about 0.2 μg/ml (a total of about 1 mg in a 70 kg patient). At the recommended infusion rate, CDV would chelate this entire plasma pool in 4 minutes. In another 30-90 minutes all of the next readily available pool (8 mg in a 70 kg patient[3]) would have been consumed. Thereafter, the rate of consumption would be equal to the rate of supply — about 1 mg/day — from the next (slow replenishment[3]) pool. But this amount can be chelated by only $1/360^{th}$ of the CDV infused over that time period. Therefore the limiting factor in Zn^{++} loss is not the dose of CDV but the rate of supply to the plasma of body Zn^{++} stores — total exposure time, not total dose is the relevant parameter. The maximum infusion rate of the EDTA in ZD0859#1 is $1/200^{th}$ (greater than $1/360^{th}$) of the CDV EDTA infusion rate. Therefore it too will saturate the slow plasma Zn^{++} replenishment mechanism and therefore, after the first day or so of use, its effect on Zn^{++} depletion is also determined by total infusion time, not total infusion dose. If there is a risk of clinically significant Zn^{++} depletion by CDV after 5 days there is a risk of clinically significant Zn^{++} depletion by ZD0859#1 after about 5 days.

Table 1 shows the number of patients continuing to get study drug infusions after the 5th day. Neither urine nor plasma Zn^{++} levels were obtained in these studies. While drops in serum Zn^{++} levels with concurrent increases in urinary Zn^{++} excretion appear even on the first day of therapy with Zn^{++}-binding agents, overt signs of Zn^{++} depletion are slow to develop. The investigators were unaware of the possibility of Zn^{++} depletion and, even if they had been, the numbers of patients remaining in the study by the time overt signs of depletion might develop were too small to provide statistically meaningful information.

Table 1: Number of patients remaining in studies as a function of infusion time — all studies.

Days	6	7	8	9	10	11	12	13	14	15-21
ZD0859#1	8	6	2	2	2	2	2	1	1	0
Diprivan	7	7	4	3	3	3	2	2	2	2

1 Overview of Efficacy

The efficacy of propofol as an anesthetic agent has been established previously. The efficacy of ZD0859#1 as an anesthetic agent is not in question. Rather, efficacy depends on ZD0859#1's performance as a retardant of microbial growth *in vitro*. ZD0859#1 has been shown to slow the growth rate of commonly occurring bacterial pathogens by at least a factor of seven. The FDA microbiology group has verified the relevancy of this statistic.

2 Overview of Safety

2.1 Significant/Potentially Significant Events

2.1.1 Deaths

No deaths were attributed to ZD0859#1.

2.1.2 Other Significant/Potentially Significant Events

Mild, transient hypocalcemia, coincident with study drug infusion did occur in four pediatric patients receiving ZD0859#1 and in one receiving Diprivan. Because of the small doses of EDTA involved and because there was no apparent correlation with EDTA dose given, it is unlikely that EDTA was the causative agent.

2.1.3 Overdose Experience

No overdosing was documented in the studies presented. However, in one published report[1] a 16 month old child received five times the recommended dose of calcium-saturated EDTA (CDV) for 24 hours. This dosage is 1000 times greater that the anticipated dose of EDTA that would be administered in a sedative dose of ZD0859#1 given over a 24 hour period. No ill effect was reported.

3 Labeling Review

The sponsor-proposed additions to the current Diprivan label address neither Zn^{++} depletion nor risks of early renal damage as could be identified by microscopic analysis of urine sediment.

Reviewer-suggested label modifications are included under Recommendations.

4 Conclusions

ZD0859#1 appears safe for short-term use in providing anesthesia/analgesia during surgical procedures.

No adverse events attributable to EDTA were recorded during these studies. However, Zn^{++} depletion was not addressed in any protocols and none of the investigators were aware of it as a risk. The most important signs of zinc depletion in the hospital population — poor wound healing, development of bedsores and rashes — are so common that a high index of suspicion must exist before appropriate diagnosis is likely. By the same token, the prevalence of these signs and the nonspecificity of their cause means that the sponsor will want to be able to assure afflicted patients and their families that ZD0859#1 was not implicated. This will require supporting laboratory data.

Co^{++} depletion was not considered either. If Co^{++} in the plasma is chelated by EDTA, it is conceivable that pernicious anemia would develop following prolonged exposure to ZD0859#1.

Microscopic examination of urine sediment also was not included in any of the protocols. Because renal damage due to EDTA is dose-dependent, it is unlikely that a statistically significant increase in the ZD0859#1 ICU groups would have been found. But because renal failure due to a wide variety of causes is common in the ICU population, exculpation of ZD0859#1 in specific cases is important.

5 Recommendations

The label for ZD0859#1 should be modified to include the information regarding effects associated with CDV as listed under Relevant Human Experience in this review. In particular the risk of Zn^{++} depletion during prolonged ICU administration and the less likely risk of renal damage should be stressed.

A schedule of laboratory studies — including microscopic examination of urine sediment — similar to those suggested during CDV treatment for less severe cases of plumbism should be recommended.

As with CDV, advice to discontinue the ZD0859#1 infusion for a period of 2 days after 5 days of use should be included. (This is also consistent with current interest

in avoidance of hyperlipidemia secondary to the Diprivan lipid load.) During the 2-day rest, Zn^{++} repletion could be undertaken.

The sponsor should immediately initiate a Phase 4 ICU usage study. (This study should also involve the pediatric age group because of the suspected increased Zn^{++} losses with decreasing body mass.) Objectives should include:

1. a 24-hour urine collection and measurement of Cu^{++}, Zn^{++}, and Co^{++} excretion as a function of dose of ZD0859#1 delivered over the first 24-hour. (Plasma levels of Zn^{++} do not correlate well with body Zn^{++} status.[3])

2. daily microscopic examination of urine sediment and comparison with a matched control group not receiving ZD0859#1.

Because neither informed consent nor randomization will be required, this study should be completed and preliminary results should be made available to the FDA very soon.

ADDITIONS TO PACKAGE INSERT:

Page 25 at end of last paragraph insert (WARNINGS):

The EDTA used in low concentration as a preservative in DIPRIVAN Injection is a strong chelator of trace metals — including zinc. Clinical studies have not been performed to measure Zn^{++} losses due to ZD0859#1. It is possible that as much as 10 mg of additional elemental zinc can be lost per day via this mechanism. For patients receiving ZD0859#1 infusions for greater than 5 days, consider discontinuing the infusion for a day to replace estimated or measured urine zinc losses.

In high doses, EDTA is toxic to the renal tubules. Urinalysis and urine sediment should be checked before each course of ICU therapy and then be monitored on alternate days during therapy.

Page 31 after second paragraph (PRECAUTIONS — Intensive Care Unit Sedation)

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Page 42 (43?) at end of Intensive Care Unit Sedation (DOSAGE AND ADMINISTRATION)

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I. L. Tyler, Ph.D./M.D. — date 4/26/96

Peer Reviewer — date 4/26/96

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HFD-170/M Wright
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HFD-340

APPENDIX — Chelation potential of disodium EDTA

I. Relevant physical chemistry data.

Table 2: Molecular weights and normal serum concentrations[8].

Substance	Molecular Weight	Serum Concentration (µg/ml)
disodium EDTA	336	0
calcium	41	96
magnesium	24	22
zinc	65	50-150 µg/dL 25 µg/kg body weight*

* Whole-body stores. (Another, more recent, preliminary study of only two subjects[3] maintains that there is a rapidly exchanged pool of ≤ 150 µg/kg probably located in the liver plus a much larger, slowly exchanged, pool of ≅ 5 mg/kg.)

The Merck Index[9] states:

> 1 gm of monosodium EDTA (M.W.=380) chelates 215 mg of $CaCO_3$ (M.W.=100). Therefore each molecule of monosodium EDTA chelates (215 mg/100 mg)/(1000 mg/380 mg) = 0.82 Ca^{++} ions.
>
> 1 gm of trisodium EDTA (M.W.=358) chelates 242 mg of $CaCO_3$. Therefore each molecule of trisodium EDTA chelates 0.87 Ca^{++} ions.
>
> The chelation potential of disodium EDTA is not stated. However, it seems reasonable to assume that the chelation potential of disodium EDTA should be somewhere between that of mono- and tri-sodium EDTA. A conservative assumption for use in the estimation of the maximum effect of disodium EDTA on Ca^{++} homeostasis is that **each molecule of disodium EDTA chelates <u>one</u> Ca^{++} ion**. This assumption is supported by the fact that edetate calcium disodium exists in an aqueous medium and is marketed as CDV for treatment of heavy metal poisoning.

II. EDTA Toxicity Risks for Bolus Doses of ZD0859#1 as might be used for induction of anesthesia or for short surgical anesthesia.

Utilizing the assumption that each molecule of disodium EDTA chelates <u>one</u> metal ion together with the data in Section I., each µg of disodium EDTA is capable of chelating

[8] The Merck Manual. 16th Edition. Edited by Berkow R. Rahway NJ. Merck & Co., Inc, 1992, pp 977, 2580-2581

[9] The Merck Index. 11th Edition. Edited by Budavari S. Rahway NJ. Merck & Co. 1989, p 3480

41/336 = 0.122 μg of Ca^{++}
24/336 = 0.0714 μg of Mg^{++}
or
65/336= 0.194 μg of Zn^{++}.

Each ml of 0.005% EDTA contains 50 μg of disodium EDTA. Consequently each ml of 0.005% EDTA is capable of chelating

50 × 0.122 = 6.1 μg of Ca^{++}
50 × 0.0714 = 3.6 μg of Mg^{++}
or
50 × 0.194 = 9.7 μg of Zn^{++}.

Propofol bolus dosages are usually specified in mg/kg. Converting the previous to mg of 1% propofol (10mg/ml), each mg of ZD0859#1 is capable of chelating

0.61 μg of Ca^{++}
0.36 μg of Mg^{++}
or
0.97 μg of Zn^{++}.

A reasonable requirement is that bolus doses of ZD0859#1 do not reduce serum Ca^{++} or Mg^{++} levels by more than 10%. Because the ionized and protein-bound portions of these elements reach equilibrium extremely rapidly, the total, rather than the ionized serum levels are appropriate.

Human blood volume is approximately 75 ml/kg so the dose in mg/kg of ZD0859#1 resulting in a 10% reduction is

[(0.1 × 96 μg/ml) (75 ml/kg)]/[0.61 μg/mg] = 1,180 mg/kg for serum Ca^{++}
[(0.1 × 22 μg/ml) (75 ml/kg)]/(0.36 μg/mg] = 458 mg/kg for serum Mg^{++}
or
[0.1 × 25 μg/kg)] / [0.97 μg/mg] = 2.58 mg/kg for whole-body Zn^{++}.

The maximum recommended bolus dose for ZD0859#1 is 3.5 mg/kg — 0.3% of the dose for which Ca^{++} , 0.8% of the dose for which Mg^{++}, and 136% of the dose for which Zn^{++} concentrations might fall by 10%. In fact, short term Zn^{++} homeostasis is not important physiologically. Furthermore, most Zn^{++} is not readily accessible for chelation and disodium EDTA undergoes renal elimination so rapidly ($\tau_{1/2}$ = 20 to 60 minutes) that virtually no Zn^{++} losses should actually occur following a bolus dose of ZD0859#1.

Neither Ca^{++} nor Mg^{++} serum homeostasis are at risk from clinically acceptable bolus doses of ZD0859#1 . Therefore, the cardiorespiratory toxicity of propofol — not EDTA

toxicity — overwhelmingly predominates overdose risks of ZD0859#1 . Zinc homeostasis appears only to be of theoretical concern *in bolus dosing*.

III. EDTA Toxicity Risks for Long-Term ZD0859#1 Infusion, ie. ICU Sedation.

Much larger quantities of ZD0859#1 may be delivered during long-term infusions. The maximum recommended infusion rate is 100 µg/kg/min = 4,320 mg/kg/month. The relevant concern, however, is not whether this loss would deplete *serum* levels of Ca^{++}, Mg^{++}, and Zn^{++} by more than 10% but whether the serum losses can be balanced by replacement either from endogenous stores or from easily-supplied exogenous stores.

A. Calcium.

There are about 130 mg/kg of exchangeable Ca^{++} in bone. This much Ca^{++} could buffer (130 mg/kg)/(0.61 µg/mg) = (130 mg/kg)/(0.61 × 10^{-3} mg/mg) = 213,115 mg/kg of ZD0859#1 . Therefore, even without parathyroid hormone stimulation of osteoclasts, exchangeable Ca^{++} could support (213,115 mg/kg)/(4,320 mg/kg/month) = 49 months of maximal ZD0859#1 infusion.

Conclusion: Calcium homeostasis is not a concern with long-term ZD0859#1 use for sedation.

B. Magnesium

EDTA does not selectively chelate Ca^{++} in the presence of Mg^{++} .[10]

Intracellular stores supply a readily available reservoir of about 1.0 mg/kg of Mg^{++} . This reservoir could buffer (1 mg/kg)/(0.36 × 10^{-3} mg/mg) = 2,778 mg/kg of ZD0859#1 . Intracellular Mg^{++} stores could therefore support (2,778 mg/kg)/(4,320 mg/kg/month) = 0.64 months or only 19 days of maximal ZD0859#1 infusion.

However, it is standard practice in the ICU to check serum Mg^{++} twice a week and add sufficient $MgSO_4$ to maintenance fluids to balance these losses. In addition, ZD0859#1 removal of Mg^{++} was based on the assumption that all the EDTA in ZD0859#1 would chelate only Mg^{++} whereas it is unlikely that *any* Mg^{++} would be chelated (Appendix B).

Conclusion: It is unlikely that Mg^{++} homeostasis is a concern with long-term ZD0859#1 use for sedation.

C. Zinc

In long-term use, it is possible that ZD0859#1 could deplete both RBC stores of Zn^{++},

[10] Wynn, JE et al: The Toxicity and Pharmacodynamics of EGTA: Oral Administration to Rats and Comparisons with EDTA; Tox. Appl. Pharm. 16, 807-817 (1970).

compromising CO_2 exchange, and the Zn^{++} in WBC's and platelets, compromising cell-mediated immunity and wound healing. There seems to be little information regarding Zn^{++} homeostasis. However, it is standard ICU practice to add a trace element package containing 4 mg (=57 μg/kg) of Zn^{++} to each day's maintenance fluids for long-term patients. This infusion rate for Zn^{++} could fully compensate for an infusion rate of ZD0859#1 of only

$$[57\ \mu g/kg/day] / [(1440\ min/day)\times(0.97\ \mu g/mg)/(1000\ \mu g/mg)\ ] = 40\ \mu g/kg/min$$

— 40% of the maximum expected infusion rate.

Conclusion: Zn^{++} homeostasis may be a concern during long-term ICU sedation with ZD0859#1. However, the fact that EDTA is tolerated in the calcium-saturated form without evidence of Zn^{++} depletion at a dosage of 1.8 gm/day × 5 days implies that maximal infusion rates of ZD0859#1 should be tolerated for five days. (The rapid clearance of EDTA, together with the slow rate of mobilization of endogenous Zn^{++} stores to the exctracellular compartment, prohibits dose-ratio-extrapolation of the CDV prescription to longer infusion periods for ZD0859#1.)

The conclusion just reached about risks of Zn^{++} depletion by ZD0859#1 were made assuming that *all* the EDTA in ZD0859#1 chelated only Zn^{++}. If other metal ions such as Ca^{++} were chelated in preference to Zn^{++}, the conclusion would have been different. It is therefore crucial to determine the relative amounts of physiologically important di- and trivalent molecules chelated by EDTA. If it could be shown that, in the presence of Ca^{++} and/or Mg^{++}, only a small fraction of the EDTA in ZD0859#1 chelated Zn^{++}, then ZD0859#1 dosing could be increased by the inverse of that fraction.

In Appendix B it is shown that just the opposite is true — in the presence of Zn^{++}, EDTA will not chelate Ca^{++} or Mg^{++} preferring instead to chelate the Zn^{++}.

APPENDIX B — Relative chelation potential of EDTA for physiologically important ions.

In vitro the chelation potential of EDTA for a particular metal ion is specified by the EDTA stability constant for that ion. The stability constant is defined as the ratio of the moles of metal-complexed EDTA to the product of the moles of free ion and free EDTA.

$$K_M = [M^{++} \bullet EDTA]/[M^{++}][EDTA]$$

The log of the stability constants for physiologically important ions in the presence of EDTA are given in Table 3. All of the values are so large that they imply almost all the EDTA added to a beaker containing any these metal ion will form chelation complexes. For example, if 1 mole of EDTA is mixed with 1 mole of Zn^{++}, only about $2 \times 10^{-13.5}$ moles of Zn^{++} will remain unchelated.

Table 3: Log of the stability constants, , for EDTA[11] listed in decreasing order.

Ion	Log K_M*
Fe^{+++}	22.4
Cu^{++}	15.8
Pb^{++}	14.9
Zn^{++}	13.5**
Co^{++}	13.3
Fe^{++}	11.4
Mn^{++}	10.8
Ca^{++}	7.7
Mg^{++}	5.7

* Corrected for pH effect, pH=7.4

** Corrected also for the hydrolysis-effect. (Because the hydrolysis-effect correction only *reduces* the numerical value of the log stability constant, its addition to the other ions in the table could only shift them lower — not higher — relative to Zn^{++}.)

In a solution containing more than one metal ion, the ratio of the proportion of each ion chelated roughly follows the ratio of the stability constants. For example, one could

[11] Reilley CN, Schmid RW, Sadek FS: Chelon approach to analysis (I): Survey of theory and Application; J Chem Ed 36,555-64 (1959).

expect on the order of $10^{15.8}/10^{7.7} \cong 10^8$ Zn^{++} ions to be chelated for each Ca^{++} ion chelated.

Table 3, therefore, can be seen to rank metal ions in order of their decreasing susceptibility to depletion by EDTA — Fe^{+++} is most susceptible while Mg^{++} is least susceptible. It can therefore be used to estimate the relative importance of the effect of EDTA on homeostasis of each of the physiologically important ions. (It should be emphasized that the data in Table 3 are for free ions *in vitro* at physiological pH. Some trace metals, notably Cu^{++} and Co^{++}, may be so tightly bound to plasma proteins *in vivo* that they are not available for chelation by EDTA. While this may be true for the 60% of Zn^{++} which is bound to plasma globulins, it is not true for the remaining 40%.)

Fe^{+++} is not physiologically important so it can be ignored. Pb^{++} is a poison — the more cleared, the better. Cu^{++} is a trace metal and may be important but there is some experimental evidence that its homeostasis may not be affected by disodium EDTA[12,13]. Co^{++} is an important trace metal, being an essential part of vitamin B_{12}. There is apparently little information regarding EDTA and Co^{++}. However, Co^{++} is present in the plasma[14] and therefore may be available for chelation. **With the possible exception of Co^{++}, then, Zn^{++} is by far the most physiologically important ion to be concerned about — at least 100 Zn^{++} ions will be chelated for each Fe^{++} ion chelated; at least 100,000,000 Zn^{++} ions will be chelated for each Ca^{++} ion chelated.** In fact, the relatively low position of Ca^{++} in this ranking is what permits CDV to be marketed as a calcium-sparing antidote for plumbism — CDV releases Ca^{++} in preference to Pb^{++}. (The relatively high position of Fe^{++} may explain the small hemosiderin deposits found in the animal pharmacology/toxicology study with beagles.)

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[12] Hammond PB, Aronson AL, Olson WC. The mechanism of mobilization of lead by EDTA. J Pharmacol Exp Therapeu 1967; 157:196-206.

[13] Perry HM, Schroeder HA. Lesions resembling vitamin B complex deficiency and urinary loss of zinc produced by ethylene-diamine Tetra-acetate. Am J Med 1957; 22, 168-172.

[14] Gradwhol's Clinical Laboratory Methods and Diagnosis 7th Edition Edited by Frankel S, Reitman S and Sonnenwirth AC, CV Mosby Co. 1970, p 469.

MEDICAL OFFICER SECONDARY REVIEW

NDA 19-627/S027

Diprivan (propofol) Injectable Emulsion

Review date April 26, 1996

Robert F. Bedford, M.D.

Division of Anesthetic, Critical Care and Addiction Drug Products
MEDICAL OFFICER SECONDARY REVIEW

NDA#:	19-627 Supplement
NAME:	Diprivan "ZD0859#1"
SPONSOR:	Zeneca
FILING DATE:	12/22/95
REVIEWER:	Robert F. Bedford, M.D.
REVIEW DATE:	April 26, 1996
CSO:	David Morgan

Introduction

Since NDA approval in 1989, Diprivan has been identified as an anesthetic that carries with it the potential for bacterial contamination and patient septicemia. Because the active ingredient, propofol, is suspended in an emulsion of Intralipid, there is always the possibility of bacterial contamination whenever a sterile ampule or vial is punctured in order to draw up a syringe-full of agent. Diprivan is administered initially as a bolus to induce anesthesia, followed by a continuous infusion for maintenance of anesthesia. If sufficient incubation time lapses between contamination of the drug and its intravenous administration, a high titer of bacterial overgrowth can occur, depending on the organism, the innoculum size and the ambient temperature. Diprivan's labeling has undergone repeated revisions over the past 6 years, along with mailing of two "Dear Doctor" letters, all of which have been aimed at advising anesthesia providers to use sterile technique, to administer only freshly drawn-up anesthetic and to discard any unused drug promptly.

Despite the above efforts, approximately 20 reports/year of Diprivan-related sepsis are received both from the FDA's spontaneous reporting system and from the sponsor's quarterly "fever report" submissions to the NDA, which were made a Phase IV commitment in response to the above problems. While the incidence of this problem is relatively small in comparison to approximately 3 million Diprivan anesthetics administered annually, FDA has continued to work with the sponsor to develop a Diprivan formulation that will not be as susceptible to bacterial overgrowth in the face of inadvertent contamination. After extensive testing, addition of .005% EDTA was found to prevent rapid multiplication of most bacterial contaminants of Diprivan. The sponsor presented these data to the Anesthetic and Life Support Drug Advisory Committee at their June 4, 1994 meeting. The committee recommended that the sponsor proceed to develop this formulation with all due deliberate speed and that FDA expedite internal review of the SNDA when it was submitted.

Review of NDA Supplement:

The clinical trials:

The sponsor submitted 5 clinical trials comparing standard Diprivan with the ZD0859#1 formulation. These are outlined in greater detail in the primary review. Trial 1 involved 99 healthy subjects anesthetized for 1 hour, using a cross-over design with a 15 day interval between anesthetics; Trial 2 was a double-blind comparative trial in patients undergoing coronary bypass graft surgery; Trial 3 was a randomized double-blind study involving 37 children (8 months to 12 years of age) undergoing general surgical procedures; Trials 4 and 5 were randomized double-blind ICU sedation trials during mechanical ventilation in 127 adult patients, with the longest infusion lasting 21 days. The maximum volume of ZD0859#1 infused was 4000 ml, although only 6 patients in these trials received propofol sedation for longer than 7 days.

Efficacy:

There was no difference between the two Diprivan formulations with regard to the dose requirement and pharmacokinetics of propofol. Thus, there is no question about the efficacy of the ZD0859#1 formulation: as an anethetic agent it is virtually indistinguishable from the original Diprivan product.

Safety:

In addition to acquisition of the usual hemodynamic and clinical chemistry data during the clinical trials, the sponsor collected specific information on calcium and magnesium levels, due to the possibility that the .005% EDTA in ZD0859#1 could cause depletion of these ions via its chelating action. As has been well-discussed in Dr. Tyler's primary review, there was little possibility that either of these ions would be affected by ZD0859#1 infusion during either short-term or long-term administration. As expected, there was no clinically relevant difference between the 2 propofol formulations in terms of any of the hemodynamic or other vital organ parameters measured during the clinical trials.

Since EDTA is a major component of Calcium Disodium Versonate (CDV), however, it is surprising that the sponsor appears to have ignored the labeling for CDV, which is used as primary treatment for lead toxicty. As Dr. Tyler's primary review highlights, a major concern of CDV therapy is zinc depletion. Bodily stores of Zn^{++} are limited and can only be mobilized slowly to circulating plasma proteins, where approximately 60% of Zn^{++} is tightly bound to globulins. Thus, during chronic infusion of ZD0859#1, as might occur during prolonged ICU sedation, it is theoretically possible that all available circulating zinc could be chelated by EDTA and excreted in the urine faster than it can be mobilized.

At doses of EDTA administered in CDV, nephrotoxicity is also recognized as a potential hazard. However, this is a dose-dependent phenomenon and, since the dose of EDTA in a typical 5-day ICU sedation protocol with ZD0859#1 is 200x lower than that administered in a course of CVD, this is not thought to be a likely hazard. Nevertheless, testing for renal tubular injury and the possibility of Zn^{++} depletion are addressed throughout the CDV labeling.

Dr. Tyler's primary review accurately points out where the potential risks of EDTA toxicity from prolonged ZD0859#1 administration correspond with the risks of a typical course of CVD treatment. In particular, the CVD label recommends a 2-day drug holiday after the first 5-day course of CVD dosing, followed by a second 5 day treatment regimen. Since these risks are potentially most critical for ICU patients, especially children, who may receive many days of Diprivan sedation, Dr. Tyler's recommendations for labeling that is compatible with the CVD label appear to be appropriate at this time. Likewise, his recommendation for Phase IV trials designed to demonstrate the safety of long-term ZD0859#1 in critically ill ICU patients appear to be a sound regulatory requirement. If the suggested Phase IV trials show no concern regarding Zn^{++} depletion, then the labeling could be modified at a later date, as appropriate.

Recommendations:
I concur with the primary reviewer that labeling changes to address the possibility of zinc depletion and nephrotoxicity are needed, as well as the need for the sponsor to pursue Phase IV studies addressing these issues.

Labeling Negotiations with Sponsor:
Dr. Tyler's labeling and Phase IV study recommendations (see primary review) were FAX'd to the sponsor on April 18, 1996. On April 25, the sponsor responded with the following wording for the PRECAUTIONS, Intensive Care Unit Sedation and DOSAGE AND ADMINISTRATION, Intensive Care Unit Sedation.

> "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 Injection Emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, DIPRIVAN Injection 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 with renal impairment, urinalysis and urine sediment should be checked before initiation of sedation and then monitored on alternate days during sedation."

Conclusions:

It is this reviewer's opinion that the theoretical risks of the ZD0859#1 formulation of Diprivan are far outweighed by the very real hazard of bacterial contamination and potential patient sepsis from inappropriate handling of the product. With implementation of the labeling changes agreed to by the sponsor it is concluded that the product is not only safe and effective as labeled, but is a marked improvement over the current Diprivan formulation.

It is furthermore concluded that completion of the Phase IV trials agreed upon with the sponsor will resolve the currently unknown issues regarding the effects of ZD0859#1 on magnesium balance during prolonged ICU sedation.

Orig NDA #19-627
HFD-170/Div File
HFD-170/RBedford
HFD-170/DMorgan
HFD-502
HFD-340
F/T by

Robert F Bedford 4/26/96
Robert F. Bedford, MD

Barbara Palmisano 4/26/96
Anesthetic Drug Group Leader

ATTACHMENT B

EXCLUSIVITY SUMMARY FOR NDA # 19-627 SUPPL #027

Trade Name: Diprivan Generic Name: Propofol

Applicant Name: Zeneca Pharmaceuticals HFD # 170

Approval Date: June 11, 1996

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES ___/ NO /_X__/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO / X /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____N/A_____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: Approximately twenty (20) reports of Diprivan related sepsis have been reported to the FDA and to the sponsor. The claim that is supported by the clinical data is that addition of .005% EDTA was found to prevent rapid multiplication of most bacterial contaminant of Diprivan.

Form OGD-011347 Revised 8/7/95

cc: Original NDA19-627/S-027 Division File/HFD-170 HFD-85 Mary Ann Holovac HFD-170/Morgan

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____3_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /_X__/ NO /___/

If yes, NDA #19-627 Drug Name: Diprivan

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety

YES /__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. **Combination product.**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_ / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency

could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredients(s) are considered to be bioavailabilty studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

N/A

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA#_____ Study #_____

NDA#_____ Study #_____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

N/A

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NDA#_____ Study #_____

NDA#_____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

N/A

Investigation #_____, Study #_____

Investigation # _____, Study #_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

N/A

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

N/A

YES /___/ NO /___/

If yes, explain: _____

_____

Signature
Title: CSO

6-11-96
Date

Signature of Office/
Division Director

6/11/96
Date

cc: Original NDA 19-627 Division File/170 HFD-85 Mary Ann Holovac
HFD-170/Morgan

ATTACHMENT C

MEDICAL OFFICER OVERVIEW OF THE FIVE ZENECA STUDIES

Prepared by: **Mary Fanning, M.D., HFD-600**
Larry Landow, M.D., HFD-170

INTRODUCTION

The five protocols submitted by Zeneca as the summary of their study designs and conduct were reviewed. Study objectives and priority as well as primary and secondary endpoints were extracted from the protocols and are summarized below. These parameters should reflect as accurately as possible the true intent of the studies. Whether this intent was achieved is considered in the HFD-170 review.

STUDY SUMMARIES

1. **Double-blind, randomized, controlled study of anesthetic efficacy of Diprivan EDTA versus Diprivan in healthy volunteers, looking at anesthetic effect, mineral homeostasis, and parathyroid function.**

   This study is described in the protocol as, primarily, a safety study.

   Design: Two-period crossover dose-response study. Period between treatments: 15 days. Each group received Diprivan and Diprivan EDTA at the below doses.

   Dosage and duration of treatment: 2 mg/kg bolus dose followed 1 hour later by 1 hour infusion of 25, 50, 100 or 200 mg/kg/min. Maximum total dose: 125 ml.

   Sample size: Diprivan n = 49; Diprivan EDTA n = 50 divided into four dosage groups.

   Primary objectives were: 1.) to determine if the range of infusion rates altered calcium levels and 2.) to evaluate calcium homeostasis and renal function. Secondary objectives were to compare efficacy of sedation.

   Endpoints for primary objectives were: Ca, Mg, PO4, K, Na, parathyroid hormone. Endpoints for secondary objectives were: loss of eyelash reflex, time to verbal contact, time to verbal commands, and concentration of EDTA.

HFD-170 Medical Officer comment: dose of 125 mg can reduce ionized calcium < 0.2% and magnesium < 0.6%, even when given as a rapid single bolus.

OGD Medical Officer comment: the maximum number of patients per drug/dose, if cross-over occurred for everyone, is 24. A study to establish similar clinical efficacy would require a much larger sample size. The adverse event rate, which is detectable but not statistically significant, is 1/24 (4.2%). This is much higher than would be clinically important and well above the expected possible difference in Diprivan (0.6%). Safety comparisons between the two components should also focus on the rate of infections observed with Diprivan versus Diprivan EDTA. This is a problem of aseptic technique and not a direct effect of the drug itself. Ethically this cannot be studied in a clinical trial but would require a surveillance program upon distribution of the drug.

2. **Double-blind, randomized, controlled study of anesthetic efficacy of Diprivan EDTA versus Diprivan in cardiac anesthesia**

Study population: Patients undergoing elective open heart surgery with good cardiac function.

Treatment groups: Diprivan with high-dose opioid, Diprivan with low-dose opioid, Diprivan EDTA with high-dose opioid, Diprivan EDTA with low-dose opioid. Maximum dose of EDTA received during the course of this study was less than 50 ml. Duration of drug exposure >4 hours.

Sample size: four study arms with ~ 25-6 in each. Total n = 102.

Primary objective was: to measure the effect of the EDTA formulation on calcium, magnesium, phosphorus, sodium, potassium and parathyroid hormone. Secondary objectives were: 1.) effect on renal function, 2.) efficacy of operative sedation and 3.) the speed and quality of recovery.

Endpoints for the primary objective were Ca, Mg, PO4, K, Na, and parathyroid hormone. For the secondary endpoints, endpoints included eyelash reflex (a surrogate of hypnosis), tachycardia, hypertension, and the need for cardiovascular medications intra-operatively. Parameters to evaluate post-operative recovery would have been affected by the concomitant medication (sufentanil) simultaneously administered.

3. **Double-blind, randomized, controlled study of anesthetic efficacy of Diprivan EDTA versus Diprivan in pediatric anesthesia**
Drug dosage: Infusion of 200 mcg/kg/in. Duration of dose > 30 minutes.

Sample size: Diprivan n=18, Diprivan EDTA n=19, total n = 37. Ages: <2 years, n = 3; ages 2 - 12 years, n=25. N = 28 completed full study, with three included only in safety analysis and six not evaluated.

Primary objective was to determine the effect on calcium and other minerals, listed in the above summary of endpoints. Secondary objectives included: 1.) pharmacokinetic profile, 2.) safety and efficacy when used for

maintenance sedation and 3.) measurements of the concentration of the additive (EDTA).

Endpoint measurements were similar to those listed for the studies above where these similar parameters were observed.

HFD-170 comment: Transient hypocalcemia observed only at 15 minute measurement; Diprivan 1 (6%) vs. Diprivan EDTA 4 (22%).

4. **Double-blind, randomized, controlled study of anesthetic efficacy of Diprivan EDTA versus Diprivan in the post-surgical ICU**

(See summary for study number 5)

Primary objective was to measure the effect on calcium, phosphorus, magnesium, sodium, and potassium. Secondary objectives were: 1.) to measure the effect on renal function, 2.) to evaluate comparative efficacy when used for sedation, and 3.) To measure the safety aspects of sedation with the two formulations.

Primary endpoints were Ca, Mg, PO4, K, Na. Secondary endpoints were BUN, and Cr, arterial blood gases, and clinical parameters i.e., sedation score, stress response group, hemodynamic measurements and ventilator parameters.

5. **Double-blind, randomized, controlled study of anesthetic efficacy of Diprivan EDTA versus Diprivan in long term ICU ventilation**

The results from study number 4 and number 5 were pooled in the medical officer review.

Dosage and duration of treatment: Infusion rates ranged from 2 to 75 ug/kg. Treatment duration ranged from 3 hours to 21 days. Total dose received ranged from 80,000 to 150,000 mg, i.e., 8 to 15,000 ml Diprivan

Maximum dose: 4,000 ml bolus. MO comments states that a 70 kg person with a 4 liter bolus could have a transient 10% drop in calcium and 25%

drop in magnesium. To maintain homeostasis in serum calcium they would be draw on endogenous sources.

Sample size: HFD-170 analysis of these two studies was done after the patient sample and outcomes were pooled to give a sample size of n=127. Diprivan n=63, Diprivan EDTA n=64. Study arms were then randomized to light or heavy sedation.

Primary objectives were to evaluate the effect of the EDTA addition on calcium, phosphorus, magnesium, potassium, sodium and parathyroid hormone. Secondary objectives were: 1.) to monitor the effect on renal function, 2.) to compare hemodynamic and other safety aspects, and 3.) To compare the effect of Diprivan +/- EDTA on the control of the stress response.

Endpoint measurements were identical to those listed for study number 4 above.

Endpoints: calcium and magnesium measured 1 and 4 hours after initiation of infusion on day 1, twice on day 2, and once daily during infusion.

Comment: no change in baseline calcium, magnesium, BUN or creatinine was observed.

ATTACHMENT D

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

Date: 15-Jan-1997 03:46pm EST
From: Curtis Wright
WRIGHTC
Dept: HFD-170 PKLN 9B45
Tel No: 301-443-4250 FAX 301-443-7068

TO: Roger Williams (WILLIAMSR)

CC: Paula Botstein (BOTSTEIN)

Subject: Critique of OGD DIprivan Document

ear Roger,

I have reviewed the OGD document dated 1/8/97.

I do not agree with its conclusions.

It is perhaps not essential that I agree, but I will do you the courtesy of providing the contrarian argument you requested.

The facts are not (I hope) in dispute. Zeneca was asked to demonstrate that the new propofol product with EDTA could be used at the same doses (equivalent efficacy) and with the same precautions (equivalent safety) as the old product. They did this by double-blind, randomized, controlled clinical trials of the old formulation tested against the new formulation. Outcome measures included examination of mineral metabolism and the usual outcome measures for anesthesia.

Had the clinical studies showed either altered efficacy (the dose was affected), altered chemistry or kinetics (destabilization of the emulsion) or altered safety (effects on cardic conduction or mineral metabolism), we would have changed the labeling of the drug or not allowed the new product on the market.

The OGD document describes four stipulations for Exclusivity:

1) New Clinical Investigations were performed, which were not bioavailability studies.

We both agree that there were new studies and they were not bioavailability studies.

2) Essential to approval.

This is a debateable point. as taken the position that sufficient information about the effects of EDTA was known to allow the addition to EDTA to propofol without any testing, or perhaps with only limited confirmatory safety studies.

The Division staff debated this point internally, and were sufficiently concerned to take the issue to the Anesthesia Advisory Committee. That Committee debated the point, and recommended that full clinical studies be performed. This might or might not appear the proper decision at this time (years later), but

was the decision that the process, properly done, offered to ZENECA.

At this time we agree that these studies were essential to approval, although we both recognize that alternative views may be expressed.

3) New Clinical Investigations

"New clincial investigations means: an investigation in humans the results of which have not been previously relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product, and do not duplicate the result that was relied on by the agency to demonstrate effectiveness or safety in a new patient population of a previously approved drug product."

This is the heart of the issue. The OGD document takes the position that "the five clinical studies performed by ZENECA did not reassess the effectiveness of propofol itself."

We agree. We think, however that these are NEW clinical investigations because;

a) The results of these studies have not been previously relied on by the FDA.

b) The results of these studies do not duplicate the result that was relied on by the agency to demonstrate effectiveness or safety in a new patient population of a previously approved drug product.

The five clinical studies DID reassess the effectiveness of the FORMULATION, assuring the division that equal doses of the drug substance propofol in the old formulation and the new formulation were of apparently equivalent effectiveness. If (a competator) had submitted the new formulation as a new drug product, the studies required to establish the efficacy and safety of the new drug product would have been similar.

This is a critical point for the agency. We are under intense pressure from both internal and external sources to reduce the number of new clinical investigations to a minimum for all applicants. We often have new formulations (and sometimes new molecular entities) where the pharmacodynamics of the drug are well known. For such agents we focus the NDA development work on studies that are optimized to collect safety data. If the sponsor faces the risk of a post-hoc determination by OGD that no exclusivity is waranted, we will end up with portfolios full of multiple Phase II efficacy studies, and the safety studies we really need will not be done.

I think the document presents a possible misreading of point 3. It appears to me to be a simple statement that if the FDA has made previous use of a study in demonstrating the efficacy or safety of a drug product, that study cannot be judged a new clinical investigation.

The studies of Diprivan done by the sponsor were done to show that the drug could be dosed like the old formulation, and that it posed no new safety hazard. The size of the proposed studies was adequate to find a serious new hazard at the 1-2% rate, roughly equivalent to the standards for a new drug product.

Point 4. We both agree that Zeneca conducted such clinical studies as were

performed.

Discussion

Believe me, I am sympathetic to all parties to this dispute.

ZENECA believes they have conducted studies in good faith and deserve exclusivity.

,et al.) believe that no studies beyond (perhaps) limited safety studies are needed to establish the safety of EDTA added to propofol.

OGD does not want to establish a precedent for "pseudo-exclusivity" where sponsors do clinical trials that the agency does not really need and then claim three more years of monopoly based on useless trials.

ORM does not want to establish a precedent of "post-hoc" disputes over exclusivity that may discourage sponsors from doing needed safety studies.

My opinon is that a proper pathway out of this dilemma is going to be hard to find. One alternative that I have not heard mentioned is to ask those that wish to make generic Diprivan with EDTA to do limited safety studies to establish that the preservative they chose to use is safe in the quantity of vehicle they must deliver and file a 505(b2) NDA. My guess is that :t. al. could have completed a proper study of the safety of the vehicle in normal volunteers looking at metals balance in the time they have spent in this dispute. Those who want to make generic Diprivan could submit a 505(b2) consiting of their already completed bio study and a limited safety study of the vehicle and get their own NDA, since we would take the position that the essential safety element of the Zeneca studies was the safety of the EDTA.

I will, of course, support the final decision of the Center. I have, as you asked, laid out the contrarian point of view.

Respectfully,

Curtis Wright