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.)

[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, MD 4/26/96

Anesthetic Drug Group Leader 4/26/96

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

Dear 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 CGD 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. Ohmeda has 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

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

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

) New Clinical Investigations

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

his is the heart of the issue. The OGD document takes the position that "the ive clinical studies performed by ZENECA did not reassess the effectiveness of ropofol itself."

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

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

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

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

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

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

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

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

erformed.

iscussion

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

ENECA believes they have conducted studies in good faith and deserve
xclusivity.

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

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

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

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

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

espectfully,

urtis Wright