CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-627/S-035

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Zeneca Pharmaceuticals,
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437

DIPRIVAN® (propofol) Injectable Emulsion
NDA 19-627

Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act, the attached information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

CERTIFICATION

Pursuant to 21 CFR section 314.53(d)(2)(ii), Zeneca Ltd., through its Agent Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc. (hereinafter for this document, "Zeneca Pharmaceuticals") certifies that U.S. Patent Nos.5,714,520; 5,731,355; 5,731,356; and 5,908,869, information relative to each of which has previously been submitted, claims the change in DIPRIVAN® (propofol) Injectable Emulsion which is the subject of this supplemental new drug application.

Paul Denerley

PAUL M. DENERLEY, Ph.D.

Exclusivity Checklist

NDA: 19-627/S-035				
Trade Name: Diprivan® Injectable Emulsion 10 mg/ml				
Generic Name: propofol				
Applicant Name: AstraZeneca LP				
Division: Anesthetic, Critical Care, and Addiction Drug Products				
Project Manager: Laura Governale, Pharm.D.				
Approval Date: February 20, 2001				
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 questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE5			
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	X	No	
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.				
Explanation:				
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:				
Explanation:				
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?	Applicant received 6 months of pediatric exclusivity.			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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 (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.	Yes	X	No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				

Drug Product	Diprivan (propofol) Injectable Emulsion			
NDA #	19-627			
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
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.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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 ingredient(s) are considered to be bioavailability 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	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
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	X
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	X

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	X
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:				
Investigation #1, Study #:	0859IL/0068			
Investigation #2, Study #:	0859US/0046			
Investigation #3, Study #:				
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	X
Investigation #2	Yes		No	X
Investigation #3	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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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	X
Investigation #2	Yes		No	X
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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"):				
Investigation #1	0859IL/0068			
Investigation #2	0859US/0046			
Investigation #3				
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.				
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	Yes	X	No	
IND#:	23,006			
Explain:				
Investigation #2	Yes	X	No	
IND#:	23,006			
Explain:				
Investigation #3	Yes		No	

IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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.)	Yes		No	X
If yes, explain:				

151

Signature of PM/CSO

Date: 2/20/01

Signature of Division Director

Date:

Attachment F

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION. UPON COMPLETION FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

Date of Written Request from FDA 4-02-99 Application Written Request was made to: NDA/~~IND~~# 19-627

Timeframe Noted in Written Request for Submission of Studies 1/31/2001

NDA# 19-627 Supplement # 035 Circle one: SE1 SE2 SE3 SE4 (SE5) SE6 SE7 SE8 SLR

Sponsor Zeneca Limited

Generic Name Propofol Trade Name Diprivan

Strength 10 mg/ml Dosage Form/Route Injection, emulsion

Date of Submission of Reports of Studies 5/21/99

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 8/19/99

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N
Were the studies submitted after the Written Request?	Y ✓	N
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y ✓	N
Were the studies responsive to the terms of the Written Request?	Y ✓	N

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity X **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
See attached	5714520	3/22/15
	5731355	3/22/15
	5731356	3/22/15

Will also apply to any NP patents & exclusivities for SE5 6/11/99

SIGNED [signature] DATE 8/11/99

cc:

Archival NDA/IND ##-### 19-627

Originator: Deputy Center Director (Review Management)
October 6, 1998

DIPRIVAN® (propofol) Injectable Emulsion

DEBARMENT CERTIFICATION

For further information regarding this section, please contact:

Gerald L. Limp
Manager, Marketed Products Group
(302) 886-8017
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ZENECA
Pharmaceuticals Group
ZENECA Pharmaceuticals / Stuart Pharmaceuticals
Business Units of ZENECA Inc.

1800 Concord Pike
Wilmington
Delaware 19897 USA

Telephone (302) 886–2132
Fax (302) 886–2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

MAY 2 1 1999

Re: DIPRIVAN® (propofol) Injectable Emulsion Pediatric Exclusivity

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.

WJK/DAG/car

DIPRIVAN® (propofol) Injectable Emulsion

FINANCIAL DISCLOSURE FROM CLINICAL INVESTIGATORS

For further information regarding this section, please contact:

Gerald L. Limp
Manager, Marketed Products Group
(302) 886-8017
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Form Approved: OMB No. Xxxx-xxxx
Expiration Date: xx/xx/xx

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 2 CFR 54.2(f).

Clinical Investigators		
	Please See Attached Reports	

☐ 2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in CFR 54.2(f)).

☐ 3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
John Goddard	Vice President, Finance & Chief Financial Ofc.
FIRM/ORGANIZATION	
Zeneca, Inc.	
SIGNATURE	**DATE**
	4-27-99

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-xxxx)
Humphrey Building, Room 531-H
200 Independence Ave., SW
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this application to this address.

FORM FDA 3454 (7/97) EF

Zeneca Doc. ID: DRU-003-004-xxxxxxx

0859US-0046-Replied to Request for Disclosure.

No Financial Arrangements

Trial No *0859US/0046*

Last	First	MI	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

0859US-0046-Replied to Request for Disclosure.

No Financial Arrangements

Trial No *0859US/0046*

Last	First	MI	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

0859US-0046 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859US/0046

Last	First	MI	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068-Replied to Request for Disclosure.

No Financial Arrangements

Trial No *0859IL/0068*

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

0859IL-0068-Replied to Request for Disclosure.

No Financial Arrangements

Trial No *0859IL/0068*

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

[redacted]

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

0859IL-0068 No Response to Request for Disclosure as of the Date of this report*

Drug ID *Diprivan*

Trial No 0859IL/0068

First	MI	Last	Suffix	Facility	Dept	Add	Add1	City	State	Zip Code

*** Indicates no sponsor payments identified by corporate accounting records**

COPY

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410

Review and Basis for Action

DATE: February 16, 2001

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: File, NDA # 19-627 SE5-035 Diprivan 1%

RE: Pediatric Supplement for induction and maintenance of anesthesia and ICU sedation

Diprivan (propofol 1% emulsion) is a parenteral sedative-hypnotic agent approved for induction and maintenance of anesthesia and for MAC (monitored anesthesia care) and ICU sedation in adults. This supplement is submitted in response to a Pediatric Written Request by the Agency dated April 22,1999. The conditions of the request were determined to have been fulfilled, and the sponsor was granted 6 months of exclusivity for this supplement.

In support of this supplement the sponsor submitted studies designed to evaluate the safety of Diprivan for use in pediatric anesthesia (newborn through 3 years of age) for induction and maintenance and [redacted]. These were reviewed during a previous cycle and are detailed in Dr. Hartwell's review and Dr. Rappaport's detailed summary of May 18, 2000. An approvable letter was issued on May 19, 2000 with labeling that reflected the conclusions that safety had been demonstrated with the regimen studied for induction of anesthesia in patients over 3 years and maintenance in patients over 2 months of age.

The detailed analyses of the randomized controlled clinical trial which was submitted in support of th[redacted] are found in the previous reviews. In this study, 327 pediatric ICU patients were randomized to receive either Diprivan 2% (113 patients), Diprivan 1% (109 patients), or a standard sedative agent (SSA) such as lorazepam, chloral hydrate, fentanyl, ketamine, morphine, or phenobarbital. Diprivan was initiated at an infusion rate of 5.5 mg/kg/hr and titrated as needed to maintain sedation at a presepecified and

standardized level. The study revealed an overrepresentation of deaths in patients undergoing ICU sedation with 2% Diprivan and 1% Diprivan compared with standard sedating agents. During the study and including the 28-day follow-up period there were 25 patient deaths: 12 (11%) in the Diprivan 2% treatment arm, 9 (8%) in the Diprivan 1% treatment arm, and 4 (4%) in the SSA treatment arm. This apparent imbalance could not be explained by any other concomitant clinical variables, such as hypotension and/or bradycardia, underlying severity of illness, concomitant drugs, demographics or treatment differences. It was the feeling of the review team that the safety of Diprivan in the sedation of pediatric patients in the ICU setting was not established by this study and that the data, while not definitive, raised safety concerns which required further evaluation. This indication was therefore not approved.

In a teleconference following the action letter of May 19, 2000 the sponsor reminded the Division of the current widespread off-label use of this product in the pediatric ICU. The sponsor was advised that until the safety of Diprivan can be further evaluated, the prescribing community should be given a clear message that Diprivan is not yet indicated for use in the pediatric ICU setting. The sponsor has agreed to cautionary language in the labeling, to the issuance of a Dear Healthcare Professional Letter and a communication program that would alert practitioners to these findings.

[redacted]

The Division in a number of communications emphasized the sponsor's commitment to study in phase 4 to "gather and assess clinical information about the use of propofol in ICU sedation in children". The sponsor was advised that this commitment would not be fulfilled by the study submitted, and that further assessment would be expected.

Regulatory Actions:

1. Approval of Supplement for anesthetic induction in children 3 years of age and over, maintenance of anesthesia in children 2 months of age and over
2. Indication for use in Pediatric ICU sedation is not granted; a Dear Healthcare Provider letter will be sent by the sponsor to target audiences; detail representatives will agree to distribute the letter and new labeling with all materials about Diprivan for 6 months.

/s/

Cynthia McCormick
2/16/01 04:06:10 PM
MEDICAL OFFICER
Approval Action--Pediatric Supplement

AstraZeneca

February 16, 2001

SENT VIA FAX and United Parcel Service

Cynthia G. McCormick, M.D.
Director
Division of Anesthetics, Critical Care,
and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 170, Room No. 9B-45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. McCormick:

Re: DIPRIVAN® (propofol) Injectable Emulsion
NDA 19-627 (S-035)
Final wording for the Dear Health Care Provider letter, Updated Communication Plan

Reference is made to the Supplemental New Drug Application (sNDA) for DIPRIVAN® (propofol) 1% Injectable Emulsion (NDA 19-627), a sedative hypnotic agent, which was previously submitted to your division on May 21, 1999, with follow-up submissions on June 10, 1999, April 13, 2000, May 5, 2000, October 11, 2000 and October 12, 2000. Reference is also made to the Agency's approvable letter dated May 19, 2000 and teleconferences on June 26, 2000, September 19, 2000, September 18, 2000, November 16, 2000 and February 7, 2001.

Please find enclosed the contents of the final version of the Dear Health Care Provider letter. As stated in our 2/8/01 fax, we plan to print up this letter and distribute in an envelope marked according to the guidance in 21 CFR 200.5 for the "Important Drug Warning" category. A mock of the envelope is attached and a pdf file is also available upon request. This printing will be in Red in the final version. A copy of the final version of the letter, envelope, and label will be submitted to this division as well as DDMAC prior to dissemination.

Per our teleconference on February 7, 2001, a revised copy of the communication plan is attached for your review.

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

If you should have any questions regarding this submission, please do not hesitate to contact me, or in my absence, Lisa DeLuca at (302) 886-5594.

Sincerely,

Lynley Donovan

Lynley K. Donovan
Associate Director
Project Management
Regulatory Affairs
(302) 886-7607
(302) 886-5243

LKD

AstraZeneca
US Regulatory Affairs

FAX

Date: February 8, 2001
Number of pages including cover sheet: 4
Re: NDA 19-627 Diprivan S-035 Edits on the Dear Healthcare Provider letter

To:	Laura Governale DACCAD	From:	Lynley Donovan Lisa V. DeLuca
Phone:	301-827-7423	Phone:	302-886-7607 or 302-886-5594
Fax phone:	301-443-7068	Fax phone:	302-886-5243
CC:			

REMARKS:

☒ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dr. Governale,
Per our teleconference yesterday, please find attached our edits to the Dear Healthcare Provider letter you provided to us. Once the text has been agreed upon, we will print up the letter and envelope following the guidance in 21 CFR 200.5 for the "Important Drug Warning" category. Prior to issuing the letter, a copy of the final version of the letter and envelope will be submitted to the agency.

In addition, we have the following clarifications we would like to make with respect to the pediatric label:

through to category.

- Per your telephone request on 2/8/01 we will remove the [redacted] ategory from Table 2 as it will not be an approved indication for Maintenance. The new Table 2 would then be as follows:

Age Range	No. of Patients	Maintenance Dosage MCG/KG/MIN	Duration minutes
2 months to 2 Years	68	199 (82 - 394)	65 (12 - 282)
2 to 12 Years	165	188 (12 - 1041)	69 (23 - 374)
>12 through 16 Years	27	161 (84 - 359)	69 (26 - 251)

- Upon further review, we would like to remove the following, from the pediatric label you provided to us, on page 21, paragraph 5 [redacted] and on page 24 paragraph 4, [redacted]

  At the present time we have no good evidence to suggest that vagal stimulation is involved in the bradycardias. This was based on initial speculation as to a possible mechanism involving a decrease in sympathetic tone. Infants, especially, depend on sympathetic tone for maintenance of cardiac output. In this regard, they tend to have higher resting heart rates than older children and adults.

If you have any further questions regarding this submission, please feel free to contact either Lisa or myself at the number listed above.

Electronic Mail Message

Date: 10/25/00 9:57:14 AM
From: Spencer Salis (SALISS)
To: Laura Governale (GOVERNALEL)
Subject: Re: Diprivan Pediatric Labeling

Laura,

The following are my comments on the Diprivan Pediatric Labeling:

U
s

Spencer

NDA: #19627/S-035

NAME: Diprivan (propofol) Injectable Emulsion

SPONSOR: AstraZeneca LP

SUBMISSION DATE: 10/11/22

TYPE OF SUBMISSION: Sponsor Agreement to Proposed Label (AE letter 05/19/00) (SLR)

REVIEWER: Patricia Hartwell, MD MBA

The sponsor has submitted this labeling revision to conform to the agency's proposed revisions contained in the AE letter of October 11, 2000. With the exception of a minor revision agreed upon by the agency and the sponsor, the submitted label contains all of the proposed language. The sponsor has been informed of and will correct this error.

Upon review, the project manager's labeling comparison between the sponsor's and the agency's labeling submissions is accurate and is a confirmation of the sponsor's acceptance of this condition of the "Approvable" action.

/S/

Patricia Hartwell, MD MBA
Medical Officer

/S/

Bob Rappaport, MD
Deputy Division Director

CC: Division File
Original NDA
HFD-170: Rappaport, Hartwell, Governale

140 page(s) of revised draft labeling has been redacted from this portion of the review.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: May 18, 2000

TO: File, NDA 19-627

FROM: Bob A. Rappaport, M.D. /S/
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

THROUGH: Cynthia G. McCormick, M.D. /S/
Director, DACCADP

RE: Supervisory Review of NDA 19-627, SE5-035, Diprivan (propfol 1% solution)

BACKGROUND:

NDA 19-627, SE5-035, for Diprivan (propfol 1% solution), was submitted byAstraZeneca Pharmaceuticals on May 21, 1999. Diprivan injectable emulsion is an intravenous sedative-hypnotic agent indicated for induction and maintenance of anesthesia or sedation. It is currently approved for the induction and maintenance of anesthesia in children aged 3 years and older, and for monitored anesthesia care (MAC) and ICU sedation only in adults.

This application is based on the available results for two controlled clinical studies: one study comparing the use of Diprivan and 2% propofol formulations to Standard Agents for sedation in the ICU; and a second study comparing Diprivan to Standard Agents for general anesthesia, induction and maintenance. The clinical studies of the safety of this new formulation have been reviewed [submitted May 5, 2000] by Patricia Hartwell, M.D. The application has also been reviewed by Stella Grosser, Ph.D. (biostatistics) and Paul L. Hepp, Pharm.D. (clinical pharmacology and

biopharmaceutics). In this memo, I will briefly review the data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the supplement.

EFFECTIVENESS:

This supplement encompasses two clinical studies: 1) Study 0859IL/0068, "A Multi-center, Comparative, Randomized Trial to Determine the Overall Safety and Efficacy of 1% Diprivan vs. 2% Diprivan vs. Standard Agents Without Disodium Edetate for Sedation of Trauma, Postsurgical, or Critically Ill Pediatric Subjects" and , 2) Study 0859US/0046, "The Safety of Diprivan (propofol) Anesthesia versus Standard Anesthetic Techniques in Pediatric Subjects less than 36 Months of Age." Neither of these studies is capable of documenting other than supportive evidence of effectiveness for Diprivan. The sponsor has proposed no claims for efficacy in their labeling changes based on this supplement.

[redacted]

Study 0859US/0046 [046]:

This was a multicenter, open-label, parallel-group, study in which patients less than 36 months of age were randomized to receive general anesthesia with either Diprivan or a standard anesthetic agent. Patients randomized to the Diprivan group were induced with either Diprivan or an inhalation agent. Induction with Diprivan was at a dose of 2.5 to 3.5 mg/kg over 20 to 30 seconds. Diprivan maintenance was at a dose of 200 to 300 mcg/kg/min. A decrease to 125 to 150 mcg/kg/min was allowed after 30 minutes. Although the sponsor has not specifically stated how they chose this dosing regimen, it is the accepted regimen for pediatric patients 3 years and older.

No primary efficacy evaluations were proposed by the sponsor as would be appropriate for this open-label study.

SAFETY:

Support for the existing labeling of Diprivan for use as a general anesthetic in pediatric patients ages 3 to 17 years is based on a pharmacokinetic study in 53 children greater than 3 years, and a safety and pharmacokinetics trial comparing Diprivan with and without EDTA in 113 subjects from birth to 17 years.

In this supplement, the safety associated with two separate uses of Diprivan has been studied separately in the two trials described above. As such, Dr. Hartwell has appropriately analyzed and presented the safety data as two separate entities. In the sedation study, Diprivan 1% and 2% were administered to 222 patients at starting rates of 5.5 to 9 mg/kg/hr, and then titrated to maintain sedation. The mean daily doses ranged from 25.4 to 162.8 mg/kg. In the general anesthesia study, 51 patients received Diprivan. The mean dose for maintenance ranged from 66.8 to 238.8 mcg/kg/min. In those patients (N=5) who received Diprivan for induction, the boluses administered ranged from 0.9 to 2 mg/kg. As per Dr. Hartwell's Table 7.3.3.2, page 31 of her review, only 1 patient in the birth to less than 2 months of age group was treated with Diprivan for maintenance in this study.

In the sedation study, the mean duration of treatment for the Diprivan treated patients was 6.2 days for the 2% group and 5.4 days for the 1% group. The vast majority of the patients were treated for one week or less. In the general anesthesia study, the mean duration of treatment was 73.6 minutes with a range from 12 to 326 minutes.

ICU Sedation Study 068:

Deaths:

Twelve (11%) of the patients treated with Diprivan 2%, 9 (8%) of the patients treated with Diprivan 1%, and 4 (4%) of the patients treated with Standard Agents died during the period starting at the initiation of sedation and going through the 28th day after sedation was discontinued. The sponsor claimed that none of the deaths was related to study drug exposure. Approximately 50% of the deaths overall occurred at three centers (1, 5 and 10). Center 5, with 17% of the study subjects, had eleven deaths, 44% of the total deaths.

Dr. Hartwell carefully reviewed the CRF's and narratives for the patients who died and assessed the relatedness of the events to study drug. She found that, while two deaths (one treated with the 1% formulation and the other with the 2% formulation) could clearly be attributed to something other than Diprivan, Diprivan could not be excluded as either a direct or indirect cause of death in each of the other cases. The sponsor attempted to explain the imbalance between the treatment and placebo groups by assessing certain clinical variables which are summarized in Dr. Hartwell's Table 8.1.1.3., page 43 of her review, reproduced below:

Table 1.

Table 8.1.1.2
Baseline Variables by Survival Status

Baseline Variable		*Alive*	*Died*
PRISM Score	Mean (median)	7.2 (6)	9.8 (10)
Intubation days prior to study	Mean (median)	4.1 (1)	7.8 (3)
Lipid administration	Yes	7% (22/299)	36% (9/25)
TPN administration	Yes	18% (54/299)	60% (15/25)
Sepsis	Yes	17% (50/299)	36% (9/25)
Triglycerides	Mean (median)	116 (87)	214 (176)
Number of concomitant diseases	≥ 2	25% (75/299)	52% (13/25)

From Sponsor's Table 2, Vol.11, Appendix H, pg. 292.

The sponsor also noted that most of the deaths were confined to Center 5, and hypothesized that the patients at that center had a poorer baseline prognosis. The sponsor then used a stepwise logistic regression to define the statistically significant baseline factors associated with mortality, excluding treatment. They found that Center, TPN (total parenteral nutrition) administration, and the PRISM [see Appendix B, page 72 of

Dr. Hartwell's review] severity of illness score, were jointly associated with mortality. Controlling for these factors statistically, they found that treatment was not associated with mortality.

Dr. Grosser states on page 2 of her statistical review:

> "The analysis by the sponsor is inconclusive. Stepwise logistic regression is a mechanical, computerized variable selection procedure that may or may not identify important predictive factors; simulation studies have shown that it often identifies variables that were designed to be uncorrelated with the outcome as being significantly associated with it. In addition, stepwise logistic regression is even more likely to give inconclusive or misleading results in situations where the proportion of deaths is relatively small and there is a high association among possible factors (which is the case here: 'number of intubation days before trial drug start, lipids administered, triglycerides and sepsis were all highly associated with TPN administration'). It is also not clear how 'center' was used in the final regression model – as 24 distinct factors, in 4 groups (center 1, 5, 10, and other), or dichotomized (5 vs. all others)."

The difference in the number of deaths at Center 5 compared to the rest of the Centers was statistically significant ($p < 0.001$). The sponsor compared the above described baseline variables between patients at Center 5 and all other patients. They found that the mean and median PRISM scores at Center 5 were slightly lower (6.11 and 5 vs. 7.66 and 7), but the difference were not statistically significant. Statistically significantly differences ($p < 0.05$), possibly indicative of "more severe baseline illness" and increased risk of mortality, were found for the Center 5 patients in comparisons of: 1) number of days of intubation (7.96 vs. 3.65); 2) percent receiving lipid administration (23% vs. 7%); 3) percent receiving TPN administration (32% vs. 19%); and, 4) percent with sepsis (25% vs. 17%). Mean triglycerides were also marginally significantly higher ($p = 0.052$) for the Center 5 patients.

However, as Dr. Grosser notes on page 3 of her review, the disproportion in the number of deaths at Center 5 is *more marked in the Diprivan treated patients*. She reports that, "The ratio of the odds of death – Diprivan to SSA [Standard Agents] – is 5.5 to 1 at center 5 and 1.8 to 1 at all other centers combined...The numbers are indeed small and the observed excess may indeed be due to chance; however, this issue can not be resolved with statistical analysis." She concludes that, "There is an excess number of deaths in the Diprivan treatment arms and in center 5 and in particular in the interaction between the two."

On March 20, 2000, the sponsor was contacted by telephone and asked to provide any additional information which might explain the higher incidence of mortality in the Diprivan treated patients. On March 24th, they responded by referencing earlier memos (dated September 22 and October 2, 1998) which noted a high incidence of death which they attributed to the critical condition of the patients at study entry. No further information regarding this matter has been received from the sponsor.

Dr. Hartwell further explored the disparity in the incidence of mortality with several analyses (see her discussion and summary tables on pages 44 through 46 of her review). She documented an association between mortality and longer duration of treatment with Diprivan, higher total dose of Diprivan, and higher mean rate of administration of Diprivan. She also documented an increased incidence of death associated with sepsis in the Diprivan groups, though this finding was not statistically significant. Finally, she found that PRISM scores were comparable across all three treatment groups, making the relative severity of illness at baseline, and the probability of mortality at the beginning of treatment, similar in each of the groups. When PRISM scores were compared for the subjects who died, all patients who subsequently died had PRISM scores at baseline that were greater than the group mean. Patients who had been treated with Standard Agents and subsequently died had PRISM scores that were higher than the group mean. The patients who subsequently died and had been treated with Diprivan, however, were equally likely to have had a PRISM score higher or lower than their group mean. Dr. Hartwell concludes, "...the findings...allow us to virtually eliminate an unequal distribution in illness severity to the Diprivan treatment groups as a causative factor in the group mortality differences."

In evaluating the relationship between dosing variables and deaths in this study, Dr. Hartwell has prepared the following table for her pending addendum:

Table 2.

Dosage Variable Comparisons – Survivors vs. Deaths						
Variable	Diprivan 2%			Diprivan 1%		
	All Subjects	Survivors	Deaths	All Subjects	Survivors	Deaths
Hours of Administration						
Mean	153	128	363	130	107	379
Median	80	74	209	81	78	141
Dose (mg/kg)						
Mean	1059	884	2517	850	658	2957
Median	461	438	1049	349	344	536
Rate (mcg/kg/min)						
Mean	111	112	104	96	95	107
Median	104	104	86	92	91	104

Greater exposure, by total cumulative dose and time, appears to be correlated with an increased risk of death; whereas rate of infusion does not. This, of course, may be explained by a simple association with more profoundly ill patients requiring treatment with higher doses of medication over greater periods of time. Indeed, the patients treated with Standard Agents who subsequently died had a mean duration of exposure to drug of 769 hours, far longer than the patients who died after exposure to Diprivan.

A further assessment of the probability of mortality associated with having experienced hypotension and bradycardia while being treated with Diprivan or Standard Agents has also been summarized in two tables to be included in Dr. Hartwell's pending addendum which are reproduced below:

Table 3.

Probability of Death in Patients with Hypotension						
Patient Population	**Hypotension Serious Adverse Event**			**Hypotension Adverse Event**		
	Diprivan 2% N = 113	*Diprivan 1% N = 109*	*SSA N = 105*	*Diprivan 2% N = 113*	*Diprivan 1% N = 109*	*SSA N = 105*
All Hypotensive Patients	5 (4%)	5 (5%)	2 (2%)	17 (15%)	19 (17%)	3 (3%)
Death <72 hours	2 (40%)	0 (0%)	1 (50%)	3 (18%)	1 (5%)	1 (33%)
Death >72 hours	1 (20%)	1 (20%)	0 (0%)	1 (6%)	2 (11%)	0 (0%)
Total Deaths in Hypotensive Patients	3 (60%)	1 (20%)	1 (50%)	4 (24%)	3 (16%)	1 (33%)

Table 4.

Probability of Death in Patients with Bradycardia						
Patient Population	**Bradycardia Serious Adverse Event**			**Bradycardia Adverse Event**		
	Diprivan 2% N = 113	*Diprivan 1% N = 109*	*SSA N = 105*	*Diprivan 2% N = 113*	*Diprivan 1% N = 109*	*SSA N = 105*
All Bradycardic Patients	3 (3%)	6 (6%)	2 (2%)	11 (10%)	12 (11%)	5 (5%)
Death <72 hours	1 (33%)	0 (0%)	0 (0%)	2 (18%)	1 (8%)	1 (20%)
Death >72 hours	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (8%)	1 (20%)
Total Deaths in Bradycardic Patients	1 (33%)	0 (0%)	1 (50%)	2 (18%)	2 (17%)	2 (40%)

This analysis documents that there is no increased probability of death associated with having experienced hypotension or bradycardia during exposure to propofol compared to Standard Agents.

Discontinuations:

For all age strata, the patients treated with Diprivan 1% had a statistically significant ($p < 0.05$) greater number (11/19, 58%) of discontinuations due to adverse events, compared to the patients treated with Diprivan 2% (3/7, 43%). The patients treated with Diprivan 2% had a statistically significant ($p < 0.01$) greater number of discontinuations due to adverse events compared to the patients treated with Standard Agents (2/4, 50%). Discontinuations due to adverse events occurred most frequently in the 2 month to 2 year old patients. The most common serious adverse events resulting in discontinuation from the trial were bradycardia and hypotension. Of note, 92% of the Diprivan treated patients withdrawn due to non-serious adverse events were discontinued because of elevated triglyceride levels. Dr. Hartwell's Table 8.1.3.2, page 42 of her review, summarizes the patients who discontinued due to adverse events.

Serious Adverse Events:

Serious adverse events were documented for 22% of the Diprivan 2%, 29% of the Diprivan 1%, and 10% of the patients treated with Standard Agents. There was a statistically significant increase in the incidence of serious adverse events between Diprivan 2% and Standard Agents and, also between Diprivan 1% and Standard Agents, $p < 0.05$ and $p < 0.001$, respectively.

The most common (occurring in at least three patients) serious adverse events in the Diprivan 2% patients were hypotension (4%), seizure (4%), sepsis (4%), withdrawal (4%), bradycardia (3%), multiple organ failure (3%), and pneumothorax (3%). In the patients treated with 1% Diprivan, the most common serious adverse events were bradycardia (6%), hypotension (5%), withdrawal (5%), cardiac arrest (4%), seizure (4%), sepsis (4%), apnea (3%), and jitteriness(3%). Pneumothorax (3%) was the most common serious adverse event in the Standard Agents group.

Dr. Hartwell's Table 8.1.2.2, page 49 of her review, reproduced below, summarizes the most common serious adverse events with all Diprivan treated patients combined, and is reproduced below:

Table 5.

Table 8.1.2.2
Serious Adverse Events by Treatment Group

Adverse Event	Diprivan (All) N = 222	SSA N = 105
	# Subjects	# Subjects
Multi-organ Failure	4 (2%)	1 (1%)
Sepsis	9 (4%)	1 (1%)
Cardiac Arrest	5 (2%)	2 (2%)
Bradycardia	9 (4%)	2 (2%)
Hypotension	10 (5%)	1 (1%)
Withdrawal	9 (4%)	0 (0%)
Jitteriness, Agitation	6 (3%)	0 (0%)
Seizure	8 (4%)	1 (1%)
Apnea	5 (2%)	1 (1%)
Pneumothorax	3 (1%)	3 (3%)

From Sponsor's Tables T14.5.1.1-14.5.3.5, Vol. 5, pp. 104-121; H9.3, Vol. 12, pg. 135.

For all Diprivan treated patients, when analyzed by age group, sepsis was the most common serious adverse event in the youngest group, birth to less than 2 months of age (44%); withdrawal, seizures and bradycardia (56%, 75%, and 56%, respectively) were the most common adverse events for the 2 months to less than 2 years group; and, hypotension (50%) and jitteriness/agitation were the most common adverse events for the 2 years to less than 12 years age group.

Dr. Hartwell describes a drug withdrawal syndrome associated with Diprivan previously reported anecdotally in the literature. This syndrome was characterized by jitteriness, warm flushing of the hands and feet, tachycardia, and an increased temperature, all occurring following rapid discontinuation of Diprivan. The syndrome resolved with reinstitution of the Diprivan infusion and did not reoccur with a more tapered weaning process. The incidence of the withdrawal syndrome was highest in the younger children as illustrated in Dr. Hartwell's Table 8.1.3.3.1, page 53 of her review, reproduced below:

Table 6.

Table 8.1.3.3.1 Incidence of Drug Withdrawal			
Age Group	**Treatment Group**		
	Diprivan 2% *N = 113*	*Diprivan 1%* *N = 109*	*Standard Agents* *N = 105*
Birth to <2 months	3/16 (19%)	2/11 (18%)	2/9 (22%)
2 months to <2 years	8/46 (17%)	8/51 (16%)	1/49 (2%)
2 years to <12 years	2/39 (5%)	4/34 (12%)	3/36 (8%)
12 years to <17 years	0/12 (0%)	0/13 (0%)	1/11 (9%)
Total	13/113 (12%)	14/109 (13%)	7/105 (7%)

From Sponsor's Table G14.1, Vol. 11, pp. 871-892

N.B. Although their was also a high incidence of apparent withdrawal syndromes in the youngest patients (birth to less than 2 months) treated with Standard Agents, these syndromes were classic for benzodiazepine or opiate withdrawal and were significantly different from the syndrome described above.

Other Adverse Events:

Dr. Hartwell's Table 8.1.4.3.a, page 59 of her review, summarizes the adverse events occurring in at least three subjects in the sedation trial. Review of that table reveals that drug withdrawal, bradycardia, hypotension and hyperlipidemia were the only events occurring with significantly increased frequency in the Diprivan treated patients.

Of interest, the incidence of hyperlipidemia is the only common adverse event which appears to occur significantly more often in one of the Diprivan treatment groups. It occurs with increased frequency in the Diprivan 1% group (13%) compared to the 2% group (5%), as was proposed by the sponsor in the development of the more concentrated product. However, Dr. Hartwell has reanalyzed the data based on her own readjudication of laboratory results, and finds far less difference between the Diprivan groups with this new data (42% vs. 38%; see further discussion under Laboratory Values, below).

Based on Dr. Hartwell's assessment, the common and drug-related adverse events for the Diprivan 2% treatment group were hypotension (17%), bradycardia (10%), and seizures (6%). For the Diprivan 1% treatment group they were hyperlipidemia (42%), drug withdrawal (28%), hypotension (16%), bradycardia (11%), apnea (6%), and seizures.

General Anesthesia Study 046:

Deaths, Discontinuations and Serious Adverse Events:

Only one patient died in during this trial. That patient underwent bypass surgery and suffered post-operative surgical complications (hemothorax and hypotension) leading to his death. Dr. Hartwell reviewed the CRF for this patient and determined that exposure to the study drug was unlikely to have been responsible for his death.

Other Adverse Events:

As per Dr. Hartwell's Table 8.1.4.3.b, page 60 of her review, adverse events occurring in two or more subjects exposed to Diprivan were uncommon and occurred with similar frequencies in the Standard Agents group. Only postoperative pain (6%) occurred with an incidence greater than 5% and more frequently in the Diprivan group.

Both Trials:

Laboratory Values:

There were no clinically relevant findings in the results of the blood gas samplings performed in the ICU sedation study.

EDTA is a known chelator of trace metals and calcium. While the ICU sedation study did reveal intermittent depletions of these metals in the Diprivan treated patients, the extent of depletion was as would be expected with exposure to EDTA. The inconclusive results of the sponsor's analysis of serum calcium and magnesium levels in the general anesthesia trial are not of concern, as clinically relevant changes would not be expected with the short term exposure to EDTA occurring in this setting.

As noted above, in the ICU sedation trial the incidence of hyperlipidemia was reported to be 7%, 13% and 1% in the Diprivan 2%, Diprivan 1%, and Standard Agents groups, respectively. This finding would be consistent with the sponsor's hypothesis that treatment with Diprivan 2% should result in a lower incidence of hyperlipidemia than treatment with Diprivan 1%. However, the study protocol did not define what level of hyperlipedemia should be considered abnormal. Dr. Hartwell reviewed the CRT's for all appropriate laboratory values. Her analysis and readjudication of the data resulted in incidences of hyperlipidemia of 38%, 42%, and 20%, bringing into question the sponsor's hypothesis.

Vital Signs:

Bradycardia and hypotension did occur with greater frequency in the Diprivan treated patients. However, these are known side effects of propofol treatment and were generally responsive to standard interventions.

Literature:

Dr. Hartwell's review of the pertinent literature revealed several safety related concerns for pediatric patients not currently noted in the Diprivan labeling. The first of these, a possible withdrawal syndrome, has been discussed above in the section on serious adverse events for the ICU sedation trial.

The second concern is regarding the use of propofol infusions in pediatric patients with respiratory infections. One article reported on five cases of metabolic acidosis and fatal myocardial failure after propofol infusion in children who had upper respiratory tract infections. All of those children had lipemic serum after starting propofol. A second article reported on two cases of children with upper respiratory tract infections who developed neurologic signs and symptoms upon discontinuation of propofol infusions. The neurologic complications resolved within two to three weeks. The presence of croup or epiglottitis was an exclusion criterion in the ICU sedation study submitted in this application.

Later reevaluation of the initial five cases described above resulted in the third concern, a hyperlipidemic syndrome with metabolic acidosis, lipemic serum, hepatomegaly, intractable hypotension and multiorgan failure. Reportedly, those patients received high doses, often exceeding 10 mg/kg/hr. A more recent survey identified another 12 fatalities in critically ill children who had received propofol infusions at rates greater than 4 mg/kg/hr for durations exceeding 48 hours.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS:

Dr. Hepp states, on page 1 of his review, "None of the diprivan clearance information reported for the general anesthesia study...is acceptable due to study design issues and analytical questions. No clearance information related to this general anesthesia study is acceptable for labeling purposes." In the analytical methods used to measure the samples for propofol, the controls and standard curves were apparently constructed using propofol rather than propofol emulsion. In Study 046, calculated clearance values were likely to be inaccurate because of early sampling, at less than one hour, in the setting of a drug which may not reach steady-state concentrations for several hours.

Also in reference to Study 046, the sponsor concluded that there are inverse relationships between age vs. propofol clearance, body surface area and clearance; and for weight vs. clearance. However, that conclusion was based on the combined results of studies 046 and 0859IL/0058 [058]. Study 058 evaluated subjects aged 0 to 16 years. When Dr. Hepp examined the results from Study 046 alone, he found that no such relationships were documented.

In both Studies 046 and 068, the frequency of arterial vs. venous sampling was not specified. Dr. Hepp has requested that that information be specified and discussed by the sponsor.

COMMENTS:

AstraZeneca Pharmaceuticals has submitted this supplementary application for Diprivan to provide evidence of safety in certain pediatric patient populations. No data has been provided that would be capable of documenting other than supportive evidence of effectiveness. The studies submitted in this application have been accepted by the Agency as the basis for a formal Pediatric Written Request for exclusivity. Diprivan has already been approved for the induction and maintenance of anesthesia in children aged 3 years and older, and for MAC and ICU sedation in adults only. The sponsor would like

---

In the General Anesthesia study, Study 046, only five patients received Diprivan for induction. Also, only one patient in the birth to less than two months of age group was treated with Diprivan for maintenance. Thus, exposure of patients less than three years of age to Diprivan for the induction and maintenance of general anesthesia, and exposure of patients less than two months of age to Diprivan for the maintenance of general anesthesia, were insufficiently robust to allow for an adequate assessment of the safety of Diprivan for those indications in those populations.

In the ICU Sedation study, Study 068, Dr. Hartwell has documented and investigated the disturbing finding of an increased incidence of mortality in the Diprivan treated patients compared to the patients treated with Standard Agents. The incidence was two (8% in the 2% Diprivan group) to nearly three (11% in the 1% Diprivan group) times higher than the incidence in the Standard Agents group (4%). While we have been unable to directly correlate these deaths with any specific effect due to Diprivan, we have also been unable to find any association other than Diprivan exposure to explain the higher mortality rate in the Diprivan treated patients.

The sponsor proposed that, based on a stepwise logistic analysis, center, TPN administration, and baseline severity of illness were associated with mortality. Using these factors as controlled variables, their analysis found that treatment was not associated with mortality. However, Dr. Grosser assessed this to be an inappropriate use of the stepwise logistic regression analysis due to the arbitrary selection of variables found to occur in this type of analysis, the relatively small proportion of deaths, and the high association among the possible factors under evaluation. In addition, Dr. Grosser commented on the disproportion in the number of deaths at Center 5 which were more common in the Diprivan treated patients. The ratio of the odds of death, comparing Diprivan to Standard Agent treated patients, is 5.5 to 1 at Center 5, but 1.8 to 1 at all the other centers combined. While acknowledging the possible effect of small numbers, she still felt capable of concluding that there were: an excess number of deaths in the Diprivan treated patients; an excess number of deaths at Center 5; and, an interaction between the two.

In addition, Dr. Hartwell was able to document that, while the patients with greater exposure to Diprivan, either by dose or time, had the highest rate of mortality within that group, this was also true, and to greater extent, for the patients treated in the Standard Agents group. As this was more than likely due to the sicker patients requiring prolonged and more intensive care, Dr. Hartwell also examined the probability that experiencing a common, clinically relevant adverse event, i.e. hypotension and bradycardia, might result in an increased mortality rate for the Diprivan group compared to the Standard Agents group. The findings did not support this hypothesis. However, the anecdotal reports of a potentially fatal syndrome in pediatric patients with upper respiratory infections that is associated with metabolic acidosis, myocardial failure, neurologic symptoms, lipemic serum, hepatomegaly, intractable hypotension, and multiorgan failure, warrant further investigation of the findings in this study.

Therefore, although we recognize that the number of patients studied was small and that this finding of an increased incidence of mortality in the Diprivan treated patients may have been due to chance alone, and while we have not established causality to Diprivan in our analyses, we feel it would be prudent at this time to not approve this product with an ICU sedation indication in the pediatric population until there is more complete documentation of its safety.

RECOMMENDATIONS:

1. This supplement is approvable, but only for the limited indication of maintenance of general anesthesia in pediatric patients ages 2 months to 3 years.

2. The labeling changes based on this supplement must reflect the limited changes in indication as described in (1) above, as well as appropriate changes to the Clinical Pharmacology, Precautions, Adverse Events, and Dosing and Administration sections of the PI.

/S/

Bob A. Rappaport, M.D.

May 18, 2000

Cc: Original NDA 19-627
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Hartwell
Grosser
Governale
HFD-850
Hepp

MEMORANDUM OF TELECON

DATE: March 2, 2000 TIME: 2:30-3:00 p.m.

APPLICATION NUMBER: NDA 19-627/S-035

BETWEEN:

Name: Judy Firor,
Connie Azumaya
Karen Thompson
Phone: 1-302-886-7539
Representing: Zeneca

AND

Name: Ramana Uppoor, Ph.D., Biopharmaceutics Team Leader
Paul Hepp, Ph.D., Biopharmaceutics Reviewer
Laura Governale, Pharm.D., Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: Biopharm issues regarding assay method

The primary objective of this meeting was to ascertain the analytical method used to assay plasma propofol levels.

Following introductions, Dr. Hepp posed the question to the sponsor regarding the analytical methodology used in the studies to construct the standard curve and controls for plasma propofol levels. More specifically, were the standard curve and controls constructed using free propofol or propofol emulsion? Also, how were the data validated?

The sponsor stated that the [redacted] Dr. Hepp questioned how this product related to the blood compatibility of the emulsion and how PK measurements were obtained. Would this free propofol assay be relevant if we do not know whether the propofol was coming out of the emulsion slowly or fast?

The sponsor stated that the [redacted]

Dr. Hepp questioned what kind of effects centrifugation had on the propofol emulsion. The sponsor stated that this study was not conducted for this pediatric submission; however, the data were probably obtained done previously with the original NDA submission. The sponsor

stated that they will fax the information to the Agency once they have contacted their British colleagues who are more familiar with this area.

Dr. Hepp adjourned the teleconference.

/S/

Laura Governale, Pharm.D.
Regulatory Project Manager

cc:
Archival NDA 19627/S-035
HFD-170/Division Files
HFD-170/P.Hepp, R.Uppoor, B.Rappaport, L.Governale

Drafted by: lg/3-30-00
Initialed by: C.Schumaker/3-30-00, R.Uppoor/3-31-00
Final: L.Governale/4-5-00
Filename: 19627(Zeneca)TCMemo030200.doc

TELECON

ZENECA Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

ZENECA

SENT VIA UPS NEXT DAY AIR

JUN 10 1999

Cynthia G. McCormick, MD
Director
Division of Anesthetics, Critical Care,
and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 170, Room No. 9B-23
5600 Fishers Lane
Rockville, MD 20857

SE5-035
BB
[illegible] AMEND

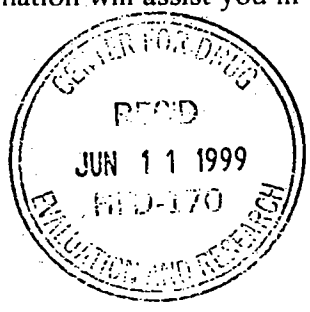
Dear Dr. McCormick:

Re: DIPRIVAN® (propofol) Injectable Emulsion
NDA 19-627 (S-035)
Pediatric Exclusivity: Pharmacokinetics for Trial 0859US/0046

Reference is made to the June 4, 1999 FDA facsimile and the June 8, 1999 teleconference to discuss the pharmacokinetic information requested by the FDA regarding the May 21, 1999 submission of Pediatric Study Reports for Pediatric Exclusivity for DIPRIVAN® (propofol) Injectable Emulsion. Present at the teleconference were Dr. Suresh Doddapaneni (Staff Fellow) and Mr. David Morgan (Project Manager) from FDA and Ms. Deborah Raybuck (Drug Disposition & Metabolism Group), Ms. Connie Azumaya (Drug Disposition & Metabolism Group) and Ms. Judy Firor (Senior Regulatory Specialist) from Zeneca.

We are pleased to provide the requested information on the pharmacokinetics of propofol in the pediatric population. The analytical methodology data for Trial 0859US/0046 (Trial 2), Appendix B, are located in Volume 15, page 247 of the May 21, 1999 submission and for your convenience another copy follows Tab 1.

In addition, the analytical methodology data for propofol from Trial 0859IL/0058 follow Tab 2. Trial 0859IL/0058 was submitted to FDA on February 16, 1998 and included a bioanalysis contribution for the quantification of EDTA in serum. We trust this information will assist you in your review of the pediatric studies for DIPRIVAN.



If I can provide further information, please do not hesitate to contact me.

Sincerely,

Gerald L. Limp
Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-8017
(302) 886-2822 (fax)

GLL/JWF/hkd
Enclosures

Desk Copy: Mr. David Morgan, HFD No. 170, Room No. 9B-45
Dr. Suresh Doddapaneni, HFD No. 870, Room No. 9B-45

FAX TRANSMISSION

Division of Anesthetic, Critical Care, And Addiction Drug Products, HFD-170

To: Mr. Gerald Limp, Manager, Marketed Products Group Date: June 4, 1999
Fax: (302) 886-2822

From: David Morgan, Regulatory Project Manger

Subject: Request for Information NDA 19-627/S-035 Diprivan (propofol) Injectable Emulsion

The reviewing pharmacokineticist has requested the following information:

(1). The analytical methodology data for blood samples obtained in study 0859US/0046 is not present in Appendix B as indicated in the main study report. Please provide the inter and intra-assay analytical method validation parameters for study 0859US/0046.

(2). Please submit the complete pharmacokinetic report of study 0859US/0046 including analytical assay validation data.

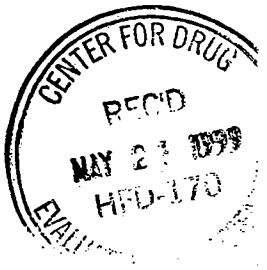
If you have questions, please contact me at, (301) 827-7410.

ZENECA Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-543;

ZENECA

May 21, 1999

HAND DELIVERED



Cynthia G. McCormick, M.D.
Director
Division of Anesthetics, Critical Care,
and Addiction Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 170, Room No. 9B-23
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. McCormick:

Re: DIPRIVAN® 1% (propofol) Injectable Emulsion
NDA 19-627

SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Reference is made to the FDA's April 22, 1999 official Written Request for submission of clinical studies for DIPRIVAN® 1% (propofol) Injectable Emulsion in pediatric patients and to the original New Drug Application (NDA) for DIPRIVAN (NDA 19-627), which was approved on October 2, 1989. DIPRIVAN is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation.

Zeneca Pharmaceuticals, a business unit of Zeneca Inc., hereby submits, in accordance with Section 111of Title 1 of the Food and Drug Administration Modernization Act (FDAMA) [Section 505A of the Federal Food, Drug, and Cosmetic Act], the enclosed Pediatric Exclusivity Submission which supports amended labeling regarding the use of DIPRIVAN in the pediatric population for general anesthesia and——. Specifically, the amended labeling involves changes to the CLINICAL PHARMACOLOGY; INDICATIONS AND USAGE; WARNINGS; PRECAUTIONS; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION sections of the full prescribing information for DIPRIVAN.

This Pediatric Exclusivity Submission consists of 24 volumes. The Index for the submission is contained within Volume 1.

The amended labeling language regarding the use of DIPRIVAN in the pediatric population is supported by the Zeneca clinical trials entitled:

- Trial 1 - A Multicenter, Comparative, Randomized Trial to Determine the Overall Safety and Efficacy of 1% Diprivan™ vs 2% Diprivan vs Standard Agents without Disodium Edetate for Sedation of Trauma, Postsurgical or Critically Ill Pediatric Subjects (Trial 0859IL/0068)

- Trial 2 - The Safety of DIPRIVAN (propofol) Anesthesia Versus Standard Anesthetic Technique in Pediatric Patients Less Than 36 months of Age (Trial 0859US/0046).

As stipulated in the Written Request, we are providing reports of the two aforementioned clinical studies and the proposed labeling changes. Pursuant to Section 111 of Title 1 of FDAMA, the enclosed information will qualify DIPRIVAN for the pediatric exclusivity extension to both the current exclusivity period (June 11, 1999) and the patent protection (March 22, 2015) for a period of six months [505A (c)(1) and (2)]. The exclusivity extension should cover a formulation of propofol containing a [redacted], not just disodium edetate.

The clinical trials in this submission were conducted under IND 23,006 and in compliance with the Institutional Review Board (IRB) requirements in 21 CFR 56, and informed consent requirements in 21 CFR 50.

As required in 21 CFR 54.4, a certification (Form FDA 3454) is enclosed regarding the financial interests and arrangements for all of the clinical investigators who contributed to the clinical trials submitted in support of this application.

Pursuant to Section 736 (a) (1) (F) of the Prescription Drug User Fee Act, a submission proposing to include a new indication for use in pediatric population is not subject to a fee. Therefore, as this submission contains such pediatric data, Zeneca Pharmaceuticals has included Form FDA 3397, User Fee Cover Sheet, and noted the user fee exclusion.

The US agent for this application will be Zeneca Pharmaceuticals, a business unit of Zeneca Inc., Wilmington, Delaware 19850-5437. The appropriate letter of authorization is enclosed.

A certification statement is enclosed which states that Zeneca Pharmaceuticals did not and will not use in any capacity the services of any person debarred under section 306(a) or (b).

In addition, the information submitted in this sNDA is considered confidential. Confidentiality of this material is hereby claimed under the provisions of 21 USC section 331(j) and 18 USC section 1905.

We trust this information will satisfy the FDA's Written Request. If you have any questions or comments, please do not hesitate to contact me.

Sincerely,

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department
(302) 886-2132
(302) 886-2822 (fax)

WJK/JWF/jr
Enclosures

Desk Copies: Ms. Indira Kumar (Cover Letter Only and 4 Desk Copies)
HFD No. 170, Room No. 9B-45

Mr. David Morgan (Cover Letter Only)
HFD No. 170, Room No. 9B-45

Mr. Douglas Sporn (Cover Letter Only) [Sent Via Fax (301) 594-0183]
HFD No. 600, Room No. 286

Dianne Murphy, M.D. (Cover Letter Only)
Health Resources and Services Administration (HRSA)
Bureau of Health Professions (BHPr)
Room No. 9A-20

Ms. Dannette Locklear (Cover Letter Only)
HFD No. 002, Room No. 6027

DIPRIVAN® (propofol) Injectable Emulsion

COPY OF FDA'S WRITTEN REQUEST

For further information regarding this section, please contact:

Gerald L. Limp
Manager, Marketed Products Group
(302) 886-8017
Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-627

APR 22 1999

Zeneca Pharmaceuticals
1800 Concord Pike
PO Box 15437
Wilmington, Delaware 19850-5437

Attention: Nigel T. Ratcliffe, Ph.D.
Assistant Director, Marketed Products Group
Drug Regulatory Affairs Department

Dear Dr. Ratcliffe:

Reference is made to your correspondence dated July 29, 1998, requesting a Written Request from the Agency for submission by Zeneca Pharmaceuticals of clinical studies of propofol in pediatric patients and your correspondence dated March 12, 1999, responding to our February 24, 1999 inadequacy letter.

To obtain needed information relating to the use of propofol in the pediatric population, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) to submit information from the following type of studies.

Type of Studies:

Trial 1: A randomized, double blind, comparative dose-ranging trial of 1% versus 2% propofol versus standard anesthetic agents requested to evaluate the safety and efficacy of propofol monotherapy in pediatric patients requiring ICU sedation.

Study Design:
This trial should enroll pediatric patients requiring mechanical ventilation and sedation for a minimum of 24 hours. Patients should be randomized to receive 1% propofol, 2% propofol or standard sedative agents (any sedative agent without disodium edetate) by continuous infusion. A validated sedation score should be recorded and dosages should be individualized and titrated so that an appropriate range of safe and effective levels can be identified.

Hemodynamics, arterial blood gases (if access lines are available), hematology and chemistry should be evaluated at baseline, during the sedation period, and if access lines are available or if clinically relevant, at post sedation.

Patients should be monitored for 24 hours after sedation for occurrence of adverse events. A global assessment of sepsis should be made at baseline and during the study period until its end.

Number of patients to be studied or power of study to be achieved:
To gain adequate assurance of the efficacy and safety of this product in the ages specified, and the doses and indication studied, approximately 300 patients should be studied.

Age group in which studies will be performed: Birth through 16 years, with substantial representation of each of the following age groups:

Birth – 2 months
2 months to 2 years
2 years – 12 years
12 years – 16 years

Clinical endpoints:
For efficacy assessment: Total daily dosage of trial medication required as determined by validated sedation score assessments.
For safety assessment: Vital signs, adverse experiences, and post-treatment physical examination.

Study evaluations:
Efficacy: Efficacy evaluations should be performed using the validated sedation score at baseline, periodically throughout the study and post treatment.

Safety: Monitoring according to standard accepted intensive care practice of mechanically ventilated patients should be performed.

Drug Specific Safety concerns: There should be an adequate attempt made to assess and document the risk of cardiovascular and neurological complications in children receiving continuous infusions of propofol.

Statistical information:
Descriptive summaries and tables of the adverse events grouped by age category (noted above) should be provided.

Labeling that may result from this study:
Changes to the Clinical Trials, Pediatric Use Section, Indications and Usage, Dosage and Administration and Adverse Reactions Sections or any other appropriate sections of the label.

Trial 2: A randomized, open-label, comparative, parallel group trial of 1% propofol versus standard anesthetic technique for induction and maintenance of general anesthesia for surgery or procedures lasting 15 minutes or more in pediatric patients from birth to 3 years of age. This study should provide data on the safety (and recovery) profile of propofol versus standard anesthetic technique, on propofol dosing for general anesthesia and on plasma concentrations of propofol in neonates, infants and children that can be correlated with effect and adverse effects.

Study Design:
This trial should enroll patients requiring general anesthesia for surgical or non-surgical procedures expected to last 15 minutes or longer, randomized to receive 1% propofol or standard sedative agents.

Group 1 – Propofol anesthesia
Group 2 – Standard anesthetic technique

Induction of anesthesia may occur with either inhalational agents or propofol. For induction, propofol should be administered by intravenous (IV) bolus followed by continuous infusion. A lower dose is recommended for patients classified as American Society of Anesthesiologists physical status III or IV. Dosages should be individualized and titrated so that an appropriate range of safe and effective levels can be identified.

Number of patients to be studied or power of study to be achieved:
To gain adequate assurance of the safety of this product in the ages specified, and the doses and indication studied, approximately 100 patients should be studied.

Age group in which studies will be performed
There should be substantial representation of each of the following age groups:

Birth – 2 months
2 months –2 years
2 years – 3years

Study evaluations:
Safety monitoring per standard accepted general anesthesia practice and plasma level monitoring where feasible.

Drug Specific Safety concerns: There should be an adequate attempt made to assess and document the risk of metabolic, cardiovascular, and neurological complications in infants receiving continuous infusions of propofol.

Statistical information: Descriptive summaries and tables of the adverse events grouped by the age should be provided.

Labeling that may result from this study:
Changes to the Clinical Pharmacokinetic Section, Clinical Trials, Pediatric Use Section, Indications and Usage, Dosage and Administration and Adverse Reactions Sections and any other appropriate sections of the label.

Format of report to be submitted:
A full study report or analysis not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. This report will conform with the *Guidelines for Format and Content of Clinical and Statistical Sections of New Drug Applications* (July 1988) and ICH E3, *Structure and Content of Clinical Study Reports* (July 1996).

Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before January 31, 2001, to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your study reports of studies in response to this written request. If you would like to extend the existing exclusivity that expires on June 11, 1999, please submit reports of studies responsive to this Written Request up to and not including the date of expiration of the exclusivity you would like to have considered for extension.

Please submit protocols of the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*) with FDA before developing pediatric protocols. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bold type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports of these pediatric studies, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Indira Kumar, Regulatory Project Manager, at (301) 827-7410.

Sincerely yours,

/S/

Victor F.C. Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research