CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-627/S060

Trade Name: Diprivan®

Generic Name: propofol

Sponsor: Fresenius Kabi USA

Approval Date: 7/9/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627/S060

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627/S060

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19627/ S-060

SUPPLEMENT APPROVAL

Fresenius Kabi USA, LLC
Attention: Dale Carlson
Senior Director, Regulatory Affairs
Three Corporate Drive
Lake Zurich, Illinois 60047

Dear Mr. Carlson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 9, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diprivan® (propofol) Injectable Emulsion.

We acknowledge receipt of your amendments dated April 10, 2013 and June 28, 2013.

The June 28, 2013 amendment constituted a commitment to revise the container and carton labeling within 6 months.

This "Changes Being Effected in 30 Days" supplemental new drug application provides to change the packaging configuration for 20 X 50 mL and 10 X 100 mL Diprivan® bottles in a carton from horizontal placement to upright vertical placement in the carton.

We have completed our review of this supplemental new drug application. This supplement is approved.

This supplemental new drug application provides for revisions to the labeling for Diprivan® (propofol) Injectable Emulsion.

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on January 10, 2013, except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed. Content of labeling must be identical to, except with the revisions listed, the enclosed labeling with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

REVISIONS

1. For the 20 mL vial, revise the expression of strength as the total drug content followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements, similar to the proposed labels for the 50 mL and 100 mL vials.
   For example:
   Diprivan
   (Propofol) Injectable Emulsion, USP
   200 mg per 20 mL
   (10 mg per mL)

2. For the 20 mL vial, revise the statement "FOR I.V. ADMINISTRATION" to read "FOR INTRAVENOUS ADMINISTRATION," similar to the proposed labels for the 50 mL and 100 mL vials.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 19627/S-060**." Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Acting Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE(S):
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH RAGHAVACHARI
07/09/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627/S060

LABELING

NDC 63323-269-50 260950

DIPRIVAN®

(Propofol) INJECTABLE EMULSION, USP

500 mg per 50 mL
(10 mg per mL)

FOR INTRAVENOUS ADMINISTRATION

SHAKE WELL BEFORE USING

Twenty 50 mL vials

For Single Patient Use Only

- Use strict aseptic technique
- **Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening**

Rx only

APP

LOT

EXP

NDC 63323-269-50 260950

DIPRIVAN®

(Propofol) INJECTABLE EMULSION, USP

500 mg per 50 mL
(10 mg per mL)

FOR INTRAVENOUS ADMINISTRATION

SHAKE WELL BEFORE USING

Twenty 50 mL vials

For Single Patient Use Only

- Use strict aseptic technique
- Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening

Rx only

APP

Sterile, nonpyrogenic

SHAKE WELL BEFORE USING

Dosage: See package insert.

In addition to the active component, propofol, the formulation contains: soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and disodium edetate (0.005%); with sodium hydroxide to adjust pH.

DIPRIVAN® should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

Store between 4° to 25°C (40° to 77°F). Do not freeze.

- Use strict aseptic technique
- **Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening**

Rx only

Manufactured for:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in Austria

M027818/01
62934E

2 03 63323 269 50 4

APP

Rx only

- Use strict aseptic technique
- Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening

For Single Patient Use Only

Twenty 50 mL vials

SHAKE WELL BEFORE USING

FOR INTRAVENOUS ADMINISTRATION

500 mg per 50 mL
(10 mg per mL)

(Propofol) INJECTABLE EMULSION, USP

DIPRIVAN®

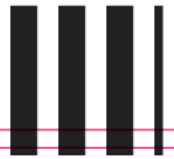
NDC 63323-269-50 260950

3036332326950 1

Manufactured for:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in Austria

US Pat 5,714,520 5,731,355
5,731,356 5,908,869

4023470
M087920/01



- **Use strict aseptic technique**
- **Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening**

Rx only

Sterile, nonpyrogenic

SHAKE WELL BEFORE USING

Dosage: See package insert.
In addition to the active component, propofol, the formulation contains: soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and disodium edetate (0.005%); with sodium hydroxide to adjust pH.
Store between 4° to 25°C (40° to 77°F).
Do not freeze.

NDC 63323-269-50 260950

DIPRIVAN®

(Propofol) INJECTABLE EMULSION, USP

500 mg per 50 mL
(10 mg per mL)

FOR INTRAVENOUS ADMINISTRATION

50 mL - For Single Patient Use Only

LOT
EXP

NDC 63323-269-65 260965

DIPRIVAN®

(Propofol) INJECTABLE EMULSION, USP

1000 mg per 100 mL
(10 mg per mL)

FOR INTRAVENOUS ADMINISTRATION

SHAKE WELL BEFORE USING

Ten 100 mL vials

For Single Patient Use Only

- Use strict aseptic technique
- **Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening**

Rx only

APP

NDC 63323-269-65 260965
DIPRIVAN®
(Propofol) INJECTABLE EMULSION, USP
1000 mg per 100 mL
(10 mg per mL)
FOR INTRAVENOUS ADMINISTRATION
SHAKE WELL BEFORE USING
Ten 100 mL vials
For Single Patient Use Only
• Use strict aseptic technique
• Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening
Rx only
APP

2 03 63323 269 65 8

NDC 63323-269-65 260965
DIPRIVAN®
(Propofol) INJECTABLE EMULSION, USP
1000 mg per 100 mL
(10 mg per mL)
FOR INTRAVENOUS ADMINISTRATION
SHAKE WELL BEFORE USING
Ten 100 mL vials
For Single Patient Use Only
• Use strict aseptic technique
• Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening
Rx only
APP

LOT

EXP

Sterile, nonpyrogenic

SHAKE WELL BEFORE USING

Dosage: See package insert.

In addition to the active component, propofol, the formulation contains: soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and disodium edetate (0.005%); with sodium hydroxide to adjust pH.

DIPRIVAN® should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

Store between 4° to 25°C (40° to 77°F). Do not freeze.

- Use strict aseptic technique
- **Contains EDTA, which inhibits microbial growth up to 12 hours, discard within 12 hours of opening**

Rx only

Manufactured for:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173
Made in Austria

DIPRIVAN is a trademark of APP Pharmaceuticals, LLC.

M02782O/01
62936E

CENTER FOR DRUG EVALUATION AND RESEARCH

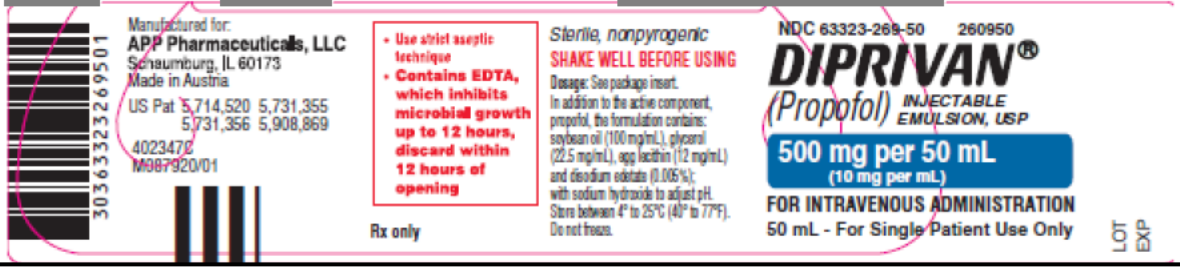
APPLICATION NUMBER:

19-627/S060

CHEMISTRY REVIEW(S)

Chemistry Review # 1	1. Division HFD-820	2. NDA Number **19-627** *EDTA formulation was approved on 06/11/1996*
3. Name and Address of Applicant Fresenius Kabi (from 01 Aug 2012) and APP (prior to 01 Aug 2012)		**4. Supplement** **Number** **Date** *S-60* *11/9/2012*
5. Name of Drug Diprivan®	**6. Nonproprietary Name** *Propofol Injectable Emulsion USP*	
7. CBE30 Supplement Provides for: *a change in packaging configuration in carton from horizontal to vertical placement for 50 ml and 100 ml Diprivan infusion bottles.*		**8. Amendment(s)** *4/10/2013 and 6/28/2013*
9. Pharmacological Category *Induction and maintenance of anesthesia*	**10. How Dispensed** Rx	**11. Related Documents**
12. Dosage Form *Injectable Emulsion for IV administration*	**13. Strength** 1% (20ml, 50ml, and 100ml)	

14. Chemical Name and Structure: *Propofol is chemically 2, 6-diisopropylphenol. Propofol Injectable Emulsion contains propofol (1%), soybean oil* (b) (4) *glycerol* (b) (4) *EDTA (0.005%), and* (b) (4)



15. Comments: *S-60 provides for vial orientation change from horizontal to vertical for 50ml and 100ml vial presentations. Similar change for 20ml vial presentation filed as S-59 was approved by the agency on 10/24/12. The vial labels for 50ml and 100ml appear acceptable to DMEPA as per e-mail dated 7/3/13 from Jamie Wilkins Parker to Jani Parinda to take an AP action,* (b) (4)

16. Conclusions and Recommendations
NDA 19-627/S-60 is recommended for an AP action.

17. Name	Signature	Date
Dr. Pramoda Maturu, Ph.D, Senior Regulatory Review Chemist		
Dr. Ramesh Raghavachari, PhD, Acting Branch Chief		

File: NDA 19627s60_Diprivan_7May13

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/s/

PRAMODA K MATURU
07/08/2013

RAMESH RAGHAVACHARI
07/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627/S060

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Review

Office of New Drug Quality Assessment

Application Number: 19627/ S-060

Name of Drug: Diprivan® (propofol) Injectable Emulsion,

Applicant: Fresenius Kabi USA, LLC

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Carton and Container Labels	4/10/2012/	4/10/2012	4/14/2008 (S-046) and (b) (4) communication to the applicant

Background and Summary

NDA 19627/ S-060 was submitted as a "Changes Being Effected in 30 days" supplement, and provides for a new packaging configuration for 20 X 50 mL and 10 X 100 mL Diprivan® bottles in a carton from horizontal placement to upright vertical placement. The labels were reviewed on June 19, 2013, by Jung E. Lee, Division of Medication Error Prevention and Analysis (DMEPA) and found unacceptable. DMEPA requests were sent to the applicant on June 21, 2013. The applicant committed to implementing the requested changes within 6 months at the next printing (see amendment dated June 28, 2013).

DMEPAs recommendations:

1. For the 20 mL vial, revise the expression of strength as the total drug content followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements, similar to the proposed labels for the 50 mL and 100 mL vials.
   For example:
   Diprivan
   (Propofol) Injectable Emulsion, USP
   200 mg per 20 mL
   (10 mg per mL)

2. For the 20 mL vial, revise the statement "FOR I.V. ADMINISTRATION" to read "FOR INTRAVENOUS ADMINISTRATION," similar to the proposed labels for the 50 mL and 100 mL vials.

On (b) (4) Allison Meyer, Division of Anesthesia, Analgesia and Addiction Product sent the applicant a communication with recommendations to the labels (b) (4) (b) (4) label changes requested which are incorporated into supplement 060 managed by ONDQA. Parinda Jani indicated that ONDQA could take an Action on S-060 and all labels changes.

Label changes requested:

1. Delete the statement "Contamination can cause fever, induction/sepsis, and/or other life-threatening illness" from the container label. Removal of this statement helps to de-clutter the red boxed information and provide increased prominence to the other red boxed statements. If you think this statement is necessary from a user or safety perspective and desire to keep this statement on the label, then please provide a rationale for your decision.
2. Delete the statement "Do not use if contamination is suspected" from within the red box on the container label as this action is a standard of practice with the use of sterile injectable products. Removal of this statement helps to de-clutter the red boxed information and provides increased prominence to the remaining statements. If you think this statement is necessary from a user or safety perspective and desire to keep this statement on the label, please provide a rationale for your decision.

In addition to the (b) (4) and the boxed statements cited above, amend the following:

1. Delete the number "1%" from the principal display panel as this information does not convey useful information to the user, to help mitigate miscalculations by the user, and is not supported by the dosing and administration portion of the insert labeling. The expression of the strength as a percent forces the health care practitioner to calculate the amount of drug in a milliliter in order to accurately dose/administer the drug product. This may lead to errors in calculations. Additionally, the percentage statement does not support the dosing of this drug product as stated in the insert labeling. Dosing is based upon milligrams or micrograms of drug. Therefore, "1%" is not consistent with the units of measurement used for dosing. Furthermore, our review of databases such as Micromedex, Facts and Comparisons and Lexicomp indicate that Propofol dosing is exclusively based on milligram, milligram/kilogram, mg/kg/hour or mcg/kg/minute, thus revising all labels with a consistent expression of strength will provide clarity to the end user regarding how much Propofol is contained in the syringe. Finally, we do not anticipate that the removal of the "1%" statement

will result in pump misprogramming errors as pumps are programmed using units of measurement such as mg/mL or mcg/mL.

2. Revise the sequence of information used to identify drug products. Traditionally, the active ingredient would be followed by the dosage form and the concentration appears last. Additionally, the strength should be expressed as the total drug content followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements. For example,

   Diprivan (Propofol) Injectable Emulsion, USP
   200 mg/20 mL
   (10 g/mL)

3. We discourage the use of dangerous abbreviations such as "I.V." on label and labeling. Revise the statement "FOR I.V. ADMINISTRATION" to read "For Intravenous Administration".
4. Delete the statement, "Sterile, nonpyrogenic" from the principal display panel of the container label.
5. Revise the statement (b) (4) to read "For Single Patient Use Only" to discourage the use of this packaging configuration on multiple patients.
6. Revise the statement "Dosage: See accompanying Professional Information Brochure" to read "Dosage: See Package Insert" on the carton labeling.
7. Revise the statement, "Begin use promptly after opening: Discard within specified time limit (See package insert)" to read "Contains EDTA, which inhibits microbial growth up to 12 hours, Discard within 12 hours of assembling the syringe" to explicitly state the limited time frame for using this product and its rationale.

The CMC Changes were reviewed by Pramoda Maturu on July 8, 2013, and found to be acceptable.

Review

This comparison was done by visually comparing the April 10, 2013, carton and labeling, to the last approved labeling and the recommendations sent to the applicant for (b) (4)

The following are the assessments for each change identified:

Immediate Container Label:

1. The "1%" was removed from the principal display.
2. The drug name and strength statement was revised as requested (see item # 2 above). The strength is now expressed as total mg of drug/total mL.
3. The statement "For I.V. Administration" was change to "For Intravenous Administration".
4. The statement "Sterile nonpyrogenic" was moved to the left side.

5. The "Rx only" statement was moved from the principal display panel to the label left side.
6. The statement "Shake Well Before Using" was moved from the front panel to the left side panel.
7. The statement "single patient infusion vial" was replace with "For Single Patient Use Only"
8. The statement "contains EDTA, which inhibits microbial growth up to 12 hours" was edit with additional information. The statement "discard within 12 hours of opening" was added.
9. The statements "use strict aseptic technique; contamination can cause fever, infection/sepsis, and/or other life-threatening illness; Begin use promptly after opening, Discard within specific time limit (See package insert); and Do not use if contamination is suspected" were removed from the red box.
10. The statement Dosage "See accompanying Professional Information Brochure" was change to "see package insert". The statement "In addition to the active component, propofol, the formulation contains: soybean oil (100mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL) and dissolution edetate (0.005%) ; with sodium hydroxide to adjust pH" was added.
11. The store temperature was change from "4° to 22° C (40°to 72° F)" to "4° to 25° C (40° to 77° F)."
12. The manufacturing site was change from the front panel to the left side. Made in Italy was change to Made in Austria.
13. NDC # was changed to 63323-269-50.

Comment: Acceptable. The changes are based on DMEPAs (b) (4) label and labeling review. The changes include patient safety information. . The information that was added is giving clarifications for the use.

Carton Label: :

1. The "1%" was removed from the principal display.
2. The sequence of Established name, active ingredient and dosage form was revised to ne expressed as the total drug content followed by the concentration in a smaller sized font.
3. The statement "For I.V. Administration" was change to "For Intravenous Administration".
4. . The statement "Sterile nonpyrogenic" was moved from the front panel to the right side panel.
5. The statements "Contamination can cause fever, infection/sepsis, and/or other life-threatening illness; Begin use promptly after opening, Discard within specific time limit (See package insert); and Do not use if contamination is suspected" were removed from the red box.
6. The statement "Shake Well Before Using" was added to the front and side panels.
7. The location of the statement "For Single Patient Use Only" changed from the top front panel to the lower left in the front panel.

8. The NDC # was changed to 63323-269-50.
9. The statement Dosage "See accompanying Professional Information Brochure" was change to "see package insert.
10. The statement "DIPRIVAN Injection" was change to "DIPRIVAN ®".
11. The statement "Patients should be continuously monitored" was removed from the right side panel.
12. The store temperature was change from "4° to 22° C (40°to 72° F)" to "4° to 25° C (40° to 77° F)."

Comment: Acceptable. The changes are based on DMEPA (b) (4) **label and labeling review. The information added provides additional safety information and the new tube configurations added (20 X 50 mL and 10 X 100 mL.**

Recommendations

The changes to the carton and container labels are acceptable. The supplement is recommended for approval with the applicant's commitment to implement DMEPAs recommendations to the 20 mL vial at the next printing.

LCDR Luz E Rivera
Regulatory Project Manager
Office of New Drug Quality Assessment Date

Michael Folkendt
Chief, Project Management Staff Date
Office of New Drug Quality Assessment

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

LUZ E RIVERA
07/08/2013

MICHAEL M FOLKENDT
07/08/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 17, 2013
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Diprivan (Propofol) Injectable Emulsion, USP 500 mg/50 mL (10 mg/mL) and 1000 mg/100 mL (10 mg/mL)
Application Type/Number:	NDA 019627
Submission Number:	S-060
Applicant:	Fresenius Kabi, USA, LLC
OSE RCM #:	2013-791

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label and carton labeling for Diprivan (Propofol) (NDA 019627) for areas of vulnerability that could lead to medication errors. This major amendment proposes to change the placement of the vials within the carton from a horizontal placement to an upright vertical placement for the 20 x 50 mL and 10 x 100 mL Diprivan bottles. The proposed carton labeling that will be used to package the 50 mL and 100 mL bottles in the upright position and the proposed container label for the 50 mL vial are provided in this major amendment.

1.1 REGULATORY HISTORY

Diprivan (Propofol), an intravenous sedative-hypnotic agent, was approved on October 2, 1989. (b) (4) The product line currently includes the 20 mL, 50 mL, and 100 mL vials for intravenous infusion.

On November 9, 2012, the Applicant submitted a Changes Being Effected (CBE-30) supplement to change the packaging configuration for the 20 x 50 mL and 10 x 100 mL Diprivan bottles in a carton from horizontal placement of the vials to upright vertical placement in the carton. (b) (4)

On April 4, 2013, a teleconference was held with the Applicant in which the OND project manager indicated that DMEPA's label recommendations (b) (4) were applicable to Supplement-060. Thus on April 10, 2013, the Applicant submitted a new container label and carton labeling for Diprivan which incorporated DMEPA's recommendations from the previous review (b) (4) As a result of the new label submission, the CBE-30 was changed to a major amendment on May 7, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 4, 2011 package insert submission.

- Active Ingredient: Propofol
- Indication of Use: Induction and maintenance of anesthesia or sedation as described in Table 3 of the insert labeling.

Table 3. Indications for DIPRIVAN Injectable Emulsion

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only (see **PRECAUTIONS**)
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

- Route of administration: Intravenous
- Dosage form: White, oil-in-water emulsion
- Dose: Individualized by patient based upon indication, age and co-morbidities
- Frequency of Administration: Bolus or continuous infusion
- How Supplied: Ready-to-use single patient infusion vials of 20 mL, 50 mL, and 100 mL in concentrations of 10 mg/mL propofol
- Storage: Store between 4°C to 22°C (40°F to 72°F). Do not freeze. Shake well before use.
- Container and Closure System: (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Diprivan (propofol) medication error reports. We also reviewed the Diprivan container label and carton labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1. The search was limited to the last search date of February 1, 2012 conducted in OSE review (b) (4) (b) (4)

Table 1: FAERS Search Strategy	
Date	February 1, 2012 to April 3, 2013
Drug Names	Active Ingredient: Propofol Product Name: Diprivan
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 30 cases. Each case was reviewed for relevancy and duplication. After individual review, 23 cases were not included in the final analysis for the following reasons:

- Accidental overdose
- Drug interaction between propofol and a concomitant drug
- Anaphylactic reaction to propofol

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Carton Labeling submitted April 10, 2013 (Appendix B)
- Container Label submitted April 10, 2013 (Appendix C)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Diprivan in (b) (4) The previous review was for a prior approval supplement (b) (4) Diprivan's product line that currently consists of the 20 mL, 50 mL, and 100 mL vials for infusion. DMEPA's recommendations for th (b) (4) he Applicant was informed that the recommendations from (b) (4) should also apply to this supplement (S-060) for the vial packaging and new labels should be submitted. On April 10, 2013, the Applicant submitted revised container label and carton labeling for Diprivan single patient use only vials which incorporated all of DMEPA's previous recommendations.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

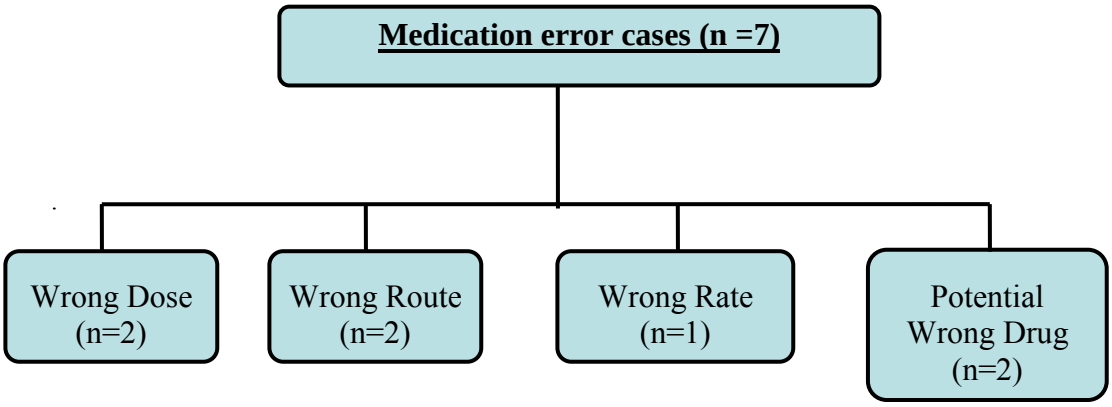
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Diprivan product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, seven Diprivan medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all case numbers for the cases summarized in this review.

Figure 1: Diprivan medication errors (n = 7) categorized by type of error



3.1.1. Wrong Dose (n=2)

We identified 2 cases of wrong dose error. In the first case (Case #8477201-5), the patient received 100 times more propofol than intended as a result of the labeling on the bottle not indicating the total drug contents. The concentration is noted as 10 mg/mL with a volume of 100 mL in the vial. This was interpreted as 10 mg/100 mL rather than 1000 mg/100 mL. The patient experienced hypotension and later death. The root cause of this error may have been the misinterpretation of the concentration statement (10 mg/mL) as the total contents of the vial. The second case (Case # 8523162-2) reported that a pump was programmed in error with the patient's previous weight resulting in the administration of the wrong dose. As a result, the patient experienced a decrease in respiratory rate which later resolved once the pump was adjusted to administer the correct dose.

We evaluated the currently approved Diprivan's container labels and carton labeling and found the concentration statement is expressed as milligrams per one milliliter instead of

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

by total concentration per total content of the vial. By not stating the total concentration of the entire contents of the vial on the label, this may lead to confusion regarding the total strength of the vial and result in a wrong dose error. Although the current labeling does not state the total concentration for the entire contents of the vial, the proposed container label and carton labeling for the 50 mL and 100 mL vials does include this information (both milligrams per total content of the vial and milligrams per one milliliter) on the principal display panel. Therefore, we find the expression of the concentration statement acceptable for the 50 mL and 100 mL vials; however, we will recommend the Applicant make similar changes to the 20 mL vial at the next printing.

3.1.2. Wrong Route (n=2)

Two cases of wrong route errors were reported. In the first case (Case #8585385-1), the patient accidentally received propofol via the intra-arterial route. The outcome was unknown and the cause of the error was not provided in the narrative. The second case (Case # 8912208-1) describes a patient who received propofol via the intrathecal route instead of intravenously. The outcome of this error was unknown and there was not enough information provided to determine the root cause.

We evaluated Diprivan's currently approved container labels and carton labeling to determine if the route of administration is clearly stated. Although the labels and labeling state Diprivan is for intravenous administration, the abbreviation "I.V." is used on the container label and carton labeling. However, we found the proposed container labels and carton labeling for the 50 mL and 100 mL vials does not include the abbreviation "I.V." and clearly state Diprivan is "For Intravenous Administration" on the principal display panel immediately below the strength statement. Therefore, we find the expression of the concentration statement acceptable for the 50 mL and 100 mL vials; however, we will recommend the Applicant make similar changes to the 20 mL vial at the next printing.

3.1.3. Wrong Rate (n=1)

One case of wrong rate error (Case #8999649-1) was identified in which the pump infusion rate of propofol was set to deliver seven times the intended dose after the nurse had changed the administration route of propofol from a syringe pump to an infusion pump. The outcome resulted in the patient experiencing a decrease in blood pressure. The root cause of this error was attributed to the nurse not following hospital guidelines which required the pump setting to be double-checked at the time of the pump and setting change which had not been done.

3.1.4. Potential Wrong Drug (n=2)

We identified 2 cases of potential wrong drug error. The reporter in the first case (Case # 8637908-1) expressed concerns over the similarity of liposomal bupivicaine to propofol due to their similar milky white appearance, similar color scheme, cap color, and similar size and shape of the vials.

We evaluated the container label and carton labeling for Exparel (bupivacaine liposome injection suspension) to determine whether the labels were sufficiently different from Diprivan's label and labeling. Our evaluation of the insert labeling found that both products come in a similar white color liquid. Exparel is described as a white to off-

white aqueous suspension while Diprivan is described as a white oil-in-water emulsion. Both products also share a similar 20 mL single use vial size. The reporter states that both products share a similar blue color scheme. Our evaluation found Exparel's container label and carton labeling for the 20 mL vial size consists of a color scheme utilizing a teal colored font on a white background for the most important information on the label (proprietary name, strength, and route of administration statements), while Diprivan's color scheme utilizes black font on a white background for the proprietary name, established name, and route of administration statement, and a white font for the strength statement surrounded by a shaded navy blue colored box.

In a National Alert Network[2] (NAN) alert dated March 20, 2012, the concern for confusion between these two products was raised due to similar physical product characteristics, milky white lipid emulsion, and colors used in the labels and packaging which could lead to confusion between the two products and potentially to medication errors with serious outcomes. (b) (4)

(b) (4)

In the second case (Case #8986754-1), the reporter states a concern with a potential mix-up between propofol and clevidipine (Cleviprex) due to their similar milky color and the difficulty of seeing/reading clevidipine's name on the label as it is printed on the hang tag. In addition, clevidipine's drug name does not appear anywhere else on the vial.

We evaluated the label and labeling for Cleviprex (clevipidine) Injectable Emulsion to determine if there was potential for confusion with Diprivan. Both products are

[2] The National Alert Network (NAN) is a coalition of members of the National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP). The network, in cooperation with the Institute for Safe Medication Practices (ISMP) and the American Society of Health-System Pharmacists (ASHP), distributes NAN alerts to warn healthcare providers of the risk for medication errors that have caused or may cause serious harm or death. NCCMERP, ISMP, and ASHP encourage the sharing and reporting of medication errors both nationally and locally, so that lessons learned can be used to increase the safety of the medication use system.

described as milky white liquid emulsions supplied in similar size vials (50 mL and 100 mL) contributing to packaging and product similarity. The reporter stated clevipidine's label was hard to see/read as the product's name was not displayed on the hang tag and did not appear anywhere else on the label. As of July 2012, the Applicant has implemented revisions to Cleviprex's 50 mL and 100 mL vial labels by adding the proprietary and established name to the body of the vials to address the problem of not having the drug name on the vial when the product was hung. As a result of these revisions to Cleviprex's container label (which allows for better identification of the drug) and no actual reports of confusion between these two products, no recommendations will be made at this time to further differentiate Diprivan's label and labeling from Cleviprex.

4 CONCLUSIONS

The Applicant proposes to change the placement of the vials within the carton from a horizontal placement to an upright vertical placement for the 20 x 50 mL and 10 x 100 mL Diprivan bottles. DMEPA concludes the proposed container label and carton labeling that will be used to package the 50 mL and 100 mL bottles in the upright position are acceptable from a medication error perspective.

5 RECOMMENDATIONS

DMEPA recommends the following be implemented prior to the approval of this NDA supplement:

5.1 COMMENTS TO THE APPLICANT

A. General Comments

1. For the 20 mL vial, revise the expression of strength as the total drug content followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements, similar to the proposed labels for the 50 mL and 100 mL vials at the next printing.

   For example:
   Diprivan
   (Propofol) Injectable Emulsion, USP
   200 mg per 20 mL
   (10 mg per mL)

2. For the 20 mL vial, revise the statement "FOR I.V. ADMINISTRATION" to read "FOR INTRAVENOUS ADMINISTRATION," similar to the proposed labels for the 50 mL and 100 mL vials at the next printing.

If you have further questions or need clarifications, please contact Teena Thomas, project manager, at 301-796-0549.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Appendix D: Case numbers discussed in this review

Case Number	FDA Rec'd Date	Medication Error	Narrative
8477201-5	4/19/2012	Wrong Dose	A report has been received from a physician concerning a 43 years old female patient.The relevant history of the patient included that the patient was admitted to hospital via the emergency department on (b) (4) presenting with symptoms of respiratory distress and hypoxemic respiratory failure. Her condition deteriorated including the development of tachyarrhythmias and subsequently required intubation. The patient also had history of shellfish allergy and three to four days history of productive cough, progressing to involved fever and night sweats.No concomitant medication or relevant history was provided.Pharmacist had a problem with Diprivan (propofol) re product labeling on the bottle where it indicated the strength 10mg/ml and contains the volume 100ml but did not contain the total strength. This caused a medication error related to that and patient had a fatality related to that. Patient died as this was interpreted 10mg in 100ml. The patient was admitted to hospital via the emergency department on (b) (4) presenting with symptoms of respiratory distress ad hypoxemic respiratory failure. Her condition detiriorated including the developement of tachyarrhythmias and subsequently required intubation.It had been reported that usually the hospital used a different agent (Hospira) for these purposes, however, due to recent drug shortages Diprivan was used. Each bottle of Diprivan displayed an additional sign (made by the hospital pharmacy), stating that each 100 ml bottle contains 1000 mg of propofol. However, a nurse administered the full bottle (1000 mg of propofol) in the IV pump, while thinking that she only administers 10 mg. In addition to standard rapid sequence intubation medications, Diprivan 1 percent injectable(1000mg/100mL) was suggested as the controlled infusion sedation agent for the intubation procedure and maintenance of sedation thereafter. The infusion pump parameters were correctly entered with a maintenance dose of 1 mg per kg per hour, but the concentration was incorrectly entered as 10 mg in 100 mL, resulted in a concentration of 0.1 mg per mL which represented 100 fold error (Preferred Term:Accidental overdose). This caused approximately 900 mg of Propofol to be infused over approximately eight minutes. No other concomitant medications were administered during this time. After the dosing error was discovered and the patient displayed the symptoms of circulatory shock, the infusion was promptly discontinued and resuscitation initiated. The resuscitation measures were unsuccessful and the patient died on (b) (4) The investigation was ongoing. The coroner had suggested that the hypotension caused by Propofol overdose might have been the leading pathophysiological mechanism leading to the development of circulatory shock Preferred Term:Shock). Autopsy results were expected in several weeks. The physician further stated that the patient was Non-smoker.Propofol was discontinued.The patient died from the event of circulatory shock on (b) (4) The outcome of the event of strength 10mg/ml was interpreted 10mg

			in 100ml resulting in a concentration of 0.1 mg/ml which represents a 100 fold error/propofol overdose was unknownThere is no information regarding the ventilation or concomitant medications. No cause of death/autopsy results are available.The company physician assessed the event circulatory shock to be serious with the serious criteria of death and event strength 10mg/ml was interpreted 10mg in 100ml resulting in a concentration of 0.1 mg/ml which represents a 100 fold error/propofol overdose to be serious with the serious criteria of fatal.Regulatory Affairs has reviewed the product labelling and provided a summary of the inner and outer label requirements with a final conclusion that the vial and carton labels comply with the regulations and Health Canadas draft Guidance Document: Labelling of Pharmaceutical Drugs for Human Use dated 07-Jul-2010.This event qualifies as a level 3 Log
8523162-2	6/21/2012	Wrong Dose	Spontaneous report received (b) (4) This case, received from a healthcare professional in Canada, involved a male patient (age unknown) who reportedly experienced accidental overdose (Accidental Overdose), incorrect dose administered (Incorrect Dose Administered) and respiratory rate decreased (Respiratory Rate Decreased) while receiving Ultiva For Injection (remifentanil hydrochloride). The patient's medical history was unknown. Concomitant medications were sodium chloride. The patient initiated Ultiva For Injection (remifentanil hydrochloride) (Mylan; intravenous, daily dose unknown, frequency unknown) on an unknown date for an unknown indication. Non-company suspect medications included propofol (intravenous, 130 mg, X1) for an unknown indication. On unknown dates, the patient experienced accidental overdose, incorrect dose administered and respiratory rate decreased. On unknown dates, accidental overdose, incorrect dose administered and respiratory rate decreased resolved. Propofol was also considered suspect. Event status at last report: Accidental Overdose (Resolved), Incorrect Dose Administered (Resolved), Respiratory Rate Decreased (Resolved) Follow-up information (received (b) (4)): On unknown dates, the patient experienced ACCIDENTAL OVERDOSE, INCORRECT DOSE ADMINISTERED and RESPIRATORY RATE DECREASED. A male infant of an unknown age, developed a decreased respiratory rate after inadvertent administration of a PROPOFOL overdose. The boy, who weighed 4.5kg, was scheduled to undergo a rigid bronchoscopy under general anesthesia with intravenous PROPFOL and REMIFENTANYL. A multichannel infusion pump was used for anesthesia maintenance. The pump was programmed to deliver PROPOFOL 300 micrograms per kilogram per minute (122.4ml per hour). However, this was based on the patient's previous weight of 68 kg [Sic]. The pump was then programmed to deliver REMIFENTANIL 0.2 micrograms per kilogram per minute (5.4ml per hour), with dosage based on the correct patient's weight of 4.5kg. The two drug infusions, in addition to NORMAL SALINE (SODIUM CHLORIDE), were then connected to his intravenous canula and started. Approximately three minutes later, he developed a decreased respiratory rate and the PROPOFOL dosage was decreased to 200 microgram per kilogram per minute (81.6ml per hour), again based on a 68 kg [Sic] body weight. Within four minutes, his bispectral index monitor showed significant burst suppression. The high infusion rate was also noted on the pump and the PROPOFOL infusion was stopped. By this time, he had received a total PROPOFOL dose of 130mg (29mg/kg). The boy regained spontaneous respiration

			within twenty minutes and the procedure was successfully completed. Within forty-five minutes, he was awake and had an uneventful recovery. Causality for PROPOFOL and REMIFENTANIL per reporter was indicated as unknown. No further information was provided, nor is expected. On unknown dates, ACCIDENTAL OVERDOSE, INCORRRECT DOSE ADMINISTERED and RESPIRATORY RATE DECREASED resolved. PROPOFOL was also considered suspect.
8585385-1	5/30/2012	Wrong Route	A report has been received from a pharmacist concerning a patient of unknown gender.No medical history and concomitant medication of the patient were reported.The patient was receiving intravenous Disoprivan (propofol) 6 ml, 1 percent which was started on an unknown date.The patient received accidental intraarterial application of Disoprivan 1 percent (preferred term:accidental exposure).The outcome of the event of accidental intraarterial application of Disoprivan 1 percent was unknown.The company physician assessed the event of accidental intraarterial application of Disoprivan 1 percent to be serious due to important medical event.
8637908-1	6/12/2012	Potential Wrong Drug	Access Number: 63915 I think it is only a matter of time until someone gets killed with this new liposomal bupivacaine product. Both are vials with a white milky I,uid inside and close in appearance to one another. The vial also has a color scheme that is quite similar to propofol labels - white with blue print. The vial cap also has a similar blue color and the vial size and shape also looks fairly similar. IV bupivacaine would be fatal. If someone doesn't mix up the vials (eg, not fully reading the when the vial label is partially turned), I'd be surprised. Knowing what goes on in ORs, it is also almost sure to happen with unlabeled syringes, as commonly seen by us in ORs on consults. This is a drug that is used in surgical patients post-op. My advice to hospitals next week is going to be DO NOT PURCHASE - UNSAFE in the OR. I really think this needs to be addressed asap by the company. I also attached one of the propofol pics.
8912208-1	11/15/2012	Wrong Route	A report has been received from a hospital physician concerning a female patient.The patient's medical history included meningeal bleeding, external ventricular derivation and brain MRI. Concomitant drugs were not provided.On unspecified date, this patient was hospitalized following meningeal bleeding. On unspecified date, external ventricular derivation was inserted to treat meningeal bleeding. At the time, patient's Glasgow coma scale was at 5. On unspecified date, brain MRI was performed. During this exam, non intentional misuse of Diprivan (propofol) once/single administration for anaesthesia. 5 ml of Diprivan were injected via intrathecal route instead of intravenous (preferred term: incorrect route of drug administration), occurred during (b) (4) Anesthesis was made aware of the mistake and 3 ml of cerebrospinal fluid were purged through the ventricular derivation. Following this drug misuse, patient's Glasgow coma scale was still at 5.Diprivan (propofol) was discontinued during (b) (4) .The outcome of the event of via intrathecal route instead of intravenous was unknown.The reporter's description of the event was as follows: spontaneous serious report transmitted by hospital physician concerning a female

			patient. This report was considered as serious, medically important event, by reporting physician. Laboratory values are available.Corrected report (b) (4) Case unsuppressed.
8986754-1	12/19/2012	Potential Wrong Drug	Description: Propofol and Clevidipine look alike in terms of their milky color. Clevidipine has a label that is difficult to see/read as it becomes the hang tag. The name of the drug is not anywhere else on the vial. Both agents cause hypotension. Line mix-ups are a concern. Pictures are attached to this report. Medication administered to or used by the patient: No Patient counseling provided: Unknown Relevant materials provided: Image
8999649-1	1/2/2013	Wrong Rate	A report has been received from a health professional (Japan Council for Quality Health Care) concerning, patient of unknown gender.The relevant history and concomitant disease of the patient were not reported.The concomitant medications of the patient were not provided.The patient was receiving Intravenous (not otherwise specified) Diprivan (propofol), 20 ml/h, started on an unknown date for sedation.After the patient came back to his/her room from an operation room, propofol was continuously administered for sedation. Blood pressure was in the range of 160 to169 mmHg, but decreased to 100 mmHg, so the dose rate of propofol 25 mL/h was decreased to 20 mL/h. Blood pressure remained in the range from 100 mmHg and 80 to 89 mmHg. Considering the exchange of drug solution in the syringe pump every two hours, the nurse changed the administration route of propofol to via infusion pump. At 17:20, blood pressure decreased (Preferred Term: Blood pressure decreased) to 68/22 mmHg. When the nurse who was beside the bed next to the patient noticed the alarm, and confirmed the infusion pump, it was found that the infusion rate of propofol in the pump was set as 130 mL/h. Approximately 4.3 mL, which corresponded to seven times more than a normal dose, of propofol had been administered (Preferred Term: Incorrect dose administered by device) in the past two minutes. Propofol was discontinued. Intravenous fluid replacement was started with maximum flow, blood pressure decreased to 44/22 mmHg. Effortil (etilefrine hydrochloride) 2 mg and Predopa(dopamine hydrochloride) were started, and then blood pressure improved. In the reporter's hospital, there had been a similar incident, so the guideline was revised. The pump setting had been supposed to be double-checked at the time of exchangeof the pump and change of the setting, but it had not been done. The instruction for confirmation of the pump setting had been made based on the guideline which was made in their own ward. The sufficient confirmation was not done at the time of shift change.Propofol was discontinued.The patient recovered from the event of blood pressure decreased on an unspecified date and the outcome of the event of incorrect dose administered by device was unknown.The company physician assessed the event of blood pressure decreased and incorrect dose administered by device to be serious with the seriousness criteria of important medical event.

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/s/

JUNG E LEE
06/17/2013

JAMIE C WILKINS PARKER
06/19/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-627/S060

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Rivera, Luz E (CDER)

From: Dale.Carlson@fresenius-kabi.com
Sent: Thursday, June 27, 2013 12:31 PM
To: Rivera, Luz E (CDER)
Cc: Raja.Agnihotram@fresenius-kabi.com
Subject: Re: sNDA 19627/ S-060

Dear Ms. Rivera,

Per your recommendation, FK USA will revise the labeling for the 20 mL Diprivan vial and implement the revised labeling within 6 months. We will submit an amendment to sNDA 19627/ S-060 with this commitment. The revised labeling will be included in the next annual report for NDA 19627.

Sincerely,

Dale Carlson
Senior Director, Regulatory Affairs

Fresenius Kabi USA
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847-550-2686
F: +1 847-550-7120
Dale.Carlson@fresenius-kabi.com
www.fresenius-kabi.us

Fresenius Kabi has Moved
New mailing address and contact information effective April 22

From: "Rivera, Luz E (CDER)" <Luz.E.Rivera@fda.hhs.gov>
To: "dale.carlson@fresenius-kabi.com" <dale.carlson@fresenius-kabi.com>,
Date: 06/21/2013 01:52 PM
Subject: sNDA 19627/ S-060

Good afternoon Mr. Carlson,

We are reviewing your supplemental New Drug Application (sNDA) 19627/ S-060 dated November 9, 2012 and additional information is needed in order to continue our evaluation.

- We recommend that the following label and labeling revisions be implemented at the next printing or within 6 months of receipt of these recommendations:

1. For the 20 mL vial, revise the expression of strength as the total drug content followed by the concentration in a smaller sized font in accordance with USP General Chapter <1> requirements, similar to the proposed labels for the 50 mL and 100 mL vials. For example:

Diprivan
(Propofol) Injectable Emulsion, USP

200 mg per 20 mL
(10 mg per mL)

2. For the 20 mL vial, revise the statement “FOR I.V. ADMINISTRATION” to read “FOR INTRAVENOUS ADMINISTRATION,” similar to the proposed labels for the 50 mL and 100 mL vials.

Please indicate by email to me (luz.e.rivera@fda.hhs.gov) and officially submit an amendment to the supplement, if your team can commit with the above comments.

Please contact me if you have any questions.

Thank you,
Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

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/s/

LUZ E RIVERA
06/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19627/ S-060

REVIEW EXTENSION – CMC SUPPLEMENT

Fresenius Kabi USA, LLC
Attention: Raja Agnihotram
Regulatory Affairs Specialist
Three Corporate Drive
Lake Zurich, Illinois 60047

Dear Mr. Agnihotram:

Please refer to your November 9, 2012 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diprivan® (propofol) Injectable Emulsion, 10 mg/mL.

We received your April 10, 2013, solicited major amendment to this application. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is July 9, 2013.

If you have any questions, call me at (301) 796- 4013.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

LUZ E RIVERA
05/07/2013

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Mail: OSE (Teena Thomas)	FROM (*Name, Office/Division, and Phone Number of Requestor*): Luz E Rivera, ONDQA, Division of Post Marketing Assessment, 301-796-4013

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/28/2013	NA	19627	S-060	11/09/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Diprivan	Standard		5/02/2013

NAME OF FIRM: Fresenius Kabi USA LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The supplement proposes a change in packaging configuration from horizontal placement to upright vertical placement. proposed printed carton are provided with the supplement

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Luz E Rivera	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

LUZ E RIVERA
03/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19627/S-60

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Fresenius Kabi USA, LLC
Attention: Dale Carlson
Senior Director, Regulatory Affairs
1501 East Woodfield Road, Suite 300E
Schaumburg, Illinois 60173

Dear Mr. Carlson:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 19627

SUPPLEMENT NUMBER: 60

PRODUCT NAME: Diprivan® (propofol) Injectable Emulsion, 10 mg/mL

DATE OF SUBMISSION: November 9, 2012

DATE OF RECEIPT: November 9, 2012

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following: to change the packaging configuration for 20 X 50 mL and 10 X 100 mL Diprivan® bottles in a carton from horizontal placement to upright vertical placement in the carton.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 8, 2013 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 9, 2013.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
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If you have questions, call me at (301) 79 4013.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

LUZ E RIVERA
11/19/2012