CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 26, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170
Through:	Kellie Taylor, Pharm.D., MPH, Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Labeling Review
Drug Name(s):	Lusedra (Fospropofol Disodium) Injection 1,050 mg/30 mL (35 mg/mL)
Application Type/Number:	NDA #: 22-244
Applicant:	MGI Pharma
OSE RCM #:	2008-1743

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b(4)

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label, carton and insert labeling are vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the presentation of the established name, product strength, and route of administration as well as the instructions for proper dosage and administration of the drug product. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) to evaluate the labeling of Lusedra Injection for the potential to contribute to medication errors. The applicant submitted revised container labels, carton and insert labeling for our review.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed the container label, carton and insert labeling for Lusedra and provided recommendations for improvement (see OSE Review #2007-2189, dated May 8, 2008). The Agency took a not approvable action on July 23, 2008, but did not forward our labeling comments to the applicant. The applicant submitted a complete response on October 13, 2008, which included revised container labels, carton and insert labeling.

1.3 PRODUCT INFORMATION

Lusedra (fospropofol disodium) is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures. b(4)

The dosage of Lusedra should be individualized and titrated to the level of sedation required for the procedure. Lusedra is administered intravenously as a bolus injection. The standard dosing regimen is an initial dose of 6.5 mg/kg with supplemental doses of 1.6 mg/kg (25% of the initial dose) as needed to achieve the desired level of sedation. The dosage of Lusedra is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh more than 90 kg should be dosed as if they are 90 kg; adults who weigh less than 60 kg should be dosed as if they are 60 kg. No initial dose should exceed 16.5 mL and no supplemental dose should exceed 4 mL.

Lusedra will be available in a 35 mg/mL concentration and supplied in single-use glass vials containing 30 mL, ready for intravenous injection. Lusedra should be stored at room temperature 20°C to 25°C (68°F to 77 °F).

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to

inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because medication error prevention staff analyze reported misuse of drugs, we staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on October 13, 2008 the following revised label and labeling for our review (see Appendices A and B for images):

- Container Label: 30 mL vial
- Carton Labeling: 30 mL vial
- Insert Labeling (no images)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the container label, carton and insert labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to the presentation of the established name, product strength, and route of administration, as well as the instructions for proper dosage and administration.

3.1.1 Container Label

[redacted] b(4)

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

7 pages Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___✓___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Risk Assessment / Risk Mitigation- 11

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 19, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products
Thru:	Claudia Karwoski, Pharm.D., Acting Director Office of Surveillance and Epidemiology/Division of Risk Management
From:	OSE Aquavan RiskMAP Review Team **Scientific Lead:** Jeanine Best, MSN, RN, PNP, Senior Drug Risk Management Analyst, OSE-DRISK Mary Dempsey, Risk Management Coordinator, OSE-DRISK Darrell Jenkins, Regulatory Project Manager, OSE-IO Martin Pollock, PharmD, Safety Evaluator, OSE-DAEA
Subject:	Risk Management Plan
Drug Name(s):	Aquavan® (fospropofol disodium) Injection
Application Type/Number:	NDA 22-244
Applicant/sponsor:	MGI Pharma, Inc.
OSE RCM #:	2007-2270

1 INTRODUCTION

This memorandum follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Aquavan® (fospropofol disodium) Injection Risk Management Plan (RiskMAP) submitted to FDA by MGI Pharma on September 26, 2007, as part of the original New Drug Application (NDA) 22-244.

Fospropofol disodium is a water-soluble, phosphono-O-methyl (POM) prodrug form of propofol, a sedative-hypnotic agent. It was submitted for the indication of: "sedation in adult patients undergoing diagnostic or therapeutic procedures [redacted] Aquavan® (fospropofol disodium) Injection 35 mg/mL will be available in single-use vials containing 1,050 mg of fospropofol disodium for intravenous injection. Relative to propofol, fospropofol has a wider therapeutic window and does not result in general anesthesia for most patients. b(4)

2 MATERIAL REVIEWED

- Risk Management Plan for Aquavan®(fospropofol disodium) Injection submitted with NDA 22-244, September 26, 2007

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

- MGI Pharma, Inc. identified the predictable drug class effects of bradycardia, hypoxemia, and hypotension as the main risks with fospropofol disodium.

- MGI Pharma, Inc. also reports that although abuse studies were not conducted with fospropofol disodium, the potential for abuse should be no greater than that seen with propofol (which is reported to be low) because fospropofol disodium has a slower time to onset of active drug effect and a more gradual rise to peak effect than propofol.[2]

Comment: Propofol is not a controlled substance under the Controlled Substance Act (CSA). The Sponsor does not propose scheduling fospropofol under the CSA because of the reasons outlined above. However, FDA Controlled Substances Staff[3] (CSS) disagrees with the Sponsor's assessment and recommends that fospropofol be considered for control under the CSA and recommends a complete and full assessment of the abuse potential of fospropofol abuse potential because of its hypnotic and sedative properties and unlike propofol, fospropofol is soluble in water which allows oral bioavailability and offers a convenient route of abuse.

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[1] See Cover Letter, NDA 22-244, Aquavan® (fospropofol disodium) Injection, September 26, 2007

[2] See Risk Management Plan, NDA 22-244, Aquavan® (fospropofol disodium) Injection, September 26, 2007

[3] See Controlled Substance Staff, Abuse Potential Assessment for NDA 22-244 (fospropofol disodium/Aquavan), March 11, 2008

3.3 PROPOSED RISK MINIMIZATION ACTIVITIES

MGI Pharma, Inc. proposes routine risk minimization activities including labeling (Package Insert, vial labeling) and routine pharmacovigilance for sedation-related adverse events along with a regular analysis of spontaneous reports, literature searches, and review of reports from the Drug Abuse Warning Network database (DAWN) to assess abuse. No additional risk minimization activities are planned at this time.

4 CONCLUSIONS

The Sponsor's submission does not constitute a formal Risk Minimization Action Plan (RiskMAP). We agree with the Sponsor that routine risk minimization activities for Aquavan® Injection are adequate at this time. Current identified and potential risks of the product appear consistent with other approved sedative-hypnotic agents used for sedation in patients undergoing diagnostic or therapeutic procedures No additional safety concerns have been identified at this time by either OSE or DAARP that warrant consideration of a formal RiskMAP..

If DAARP and/or CSS identify additional safety concerns that warrant risk minimization activities above labeling and routine pharmacovigilance, or a formal RiskMAP, please re-consult OSE/Division of Risk Management.

OSE/DMEDP (Division of Medication Error and Prevention) will provide a separate review encompassing the tradename review and potential medication errors.

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/s/

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