CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

CHEMISTRY REVIEW(S)

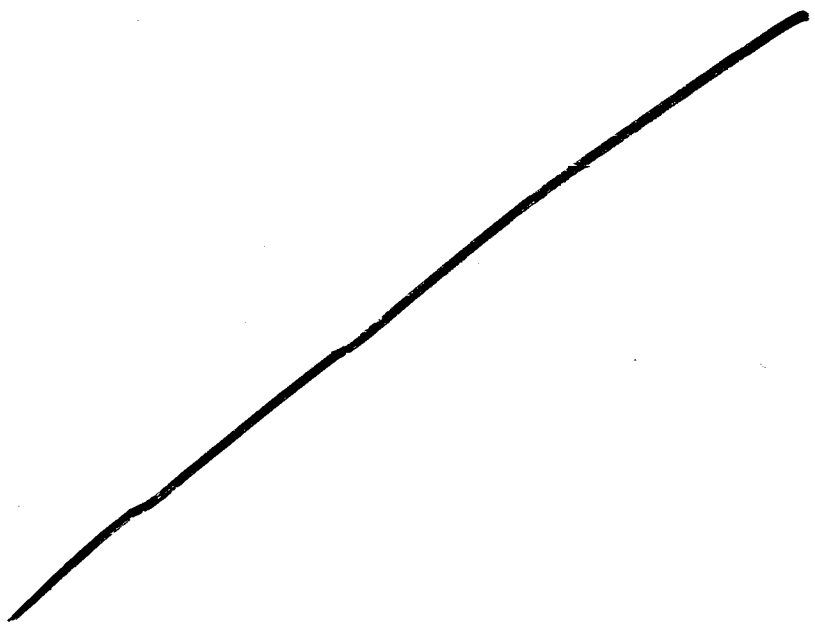
Memorandum to File

To: NDA 22-244; Lusedra™(fospropofol disodium) Injection
From: Elsbeth Chikhale, Ph.D. – Chemistry Reviewer
Subject: Resubmission dated 10/13/08 (complete amendment to Not Approval Letter)
Date: December 11, 2008

Applicant: MGI Pharma, Inc.
Proposed Proprietary Name: LUSEDRA
Established Name: fospropofol disodium
Dosage form and strength: 35 mg/mL
Route of Administration: intravenous
Indications: use as a sedative-hypnotic agent

b(4)

- Minor editorial changes were made to the CMC sections of the package insert.
- The following container and carton label were submitted on 10/13/08:



1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 4

- SPL:

LUSEDRA
fospropofol disodium injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	NDC Product Code (Source)	62856-350
Route of Administration	INTRAVENOUS	DEA Schedule	[redacted]

b(4)

INGREDIENTS

Name (Active Moiety)	Type	Strength
fospropofol disodium (fospropofol)	Active	35 MILLIGRAM In 1 MILLILITER
monothioglycerol	Inactive	
tromethamine	Inactive	

Product Characteristics

Color	Score
Shape	Size
Flavor	Imprint Code
Contains	

Packaging

# NDC	Package Description	Multilevel Packaging
1 62856-350-01	30 MILLILITER In 1 VIAL, GLASS	None

[redacted]

b(4)

Evaluation: The SPL is acceptable.

Note:
There are no remaining CMC issues, therefore NDA 22-244 is recommended for APPROVAL from CMC perspective.

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/s/

Elsbeth Chikhale
12/11/2008 09:38:13 PM
CHEMIST

Ali Al-Hakim
12/11/2008 09:52:10 PM
CHEMIST

Aquavan®
(fospropofol disodium)
Injection

NDA 22-244

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: MGI Pharma, Inc.
6611 Tributary Street
Baltimore, MD 21224

Indication: Sedation in adult patients undergoing diagnostic or therapeutic procedures.

Presentation: Aquavan® Injection is supplied as a sterile, non-pyrogenic, iso-osmotic, clear, colorless, aqueous solution of fospropofol disodium.

Each single-use, 30 mL vial is filled with 32.1 mL, intended to deliver a minimum of 30 mL, containing 1050 mg of fospropofol disodium in 30 mL of 0.25 % (w/w) monothioglycerol [redacted] and 0.12 % (w/w) TRIS [redacted] pH 8.6. Each vial is sealed with [redacted] b(4)

EER Status:		Acceptable	20-JUN-2008
Consults:	Microbiology	Acceptable	16-JUN-2008
	Pharm/Tox	Acceptable	26-JUN-2008
	EA – Categorical exclusion granted 21 CFR §25.31(b)		
	Methods Validation	Acceptable	20-JUN-2008

Original Submission: 26-SEP-2007

Post-Approval Agreements: None

Drug Substance:

The drug substance, fospropofol disodium, is a water-soluble prodrug of propofol that is converted to propofol in the body by alkaline phosphatase. Fospropofol disodium is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{13}H_{19}O_5PNa_2$, a molecular weight of 332.24, and pKa's of 1.19 and 6.27. Known chemically as 2,6-diisopropylphenoxymethyl phosphate, disodium salt, it is a [redacted] b(4)

[redacted] and is freely soluble in water [redacted] It contain no chiral centers. Polymorphism was observed but not further investigated because the drug substance will be fully dissolved in the aqueous dosage form. b(4)

[redacted] b(4)

[redacted] b(4)

Adequate stability data were provided to support a retest date [redacted] b(4)

at controlled room temperature, 20°-25°C (68°-77°F), with excursions between 15°C and 30°C.

Conclusion: Drug substance is acceptable.

Drug Product:

Aquavan® Injection is supplied as a sterile, non-pyrogenic, iso-osmotic, clear, colorless, aqueous solution of fospropofol disodium. Each single-use, 30 mL vial is filled with 32.1 mL, intended to deliver a minimum of 30 mL, containing 1050 mg of fospropofol disodium in 30 mL of 0.25 % (w/w) monothioglycerol NF [redacted] and 0.12 % (w/w) TRIS USP [redacted] pH 8.6. b(4)

[redacted] b(4)

Specification of the drug product includes: appearance, clarity, color, identification by [redacted]

b(4)

[redacted]

The provided stability data support the proposed 36 month shelf-life for the drug product packaged in the proposed container/closure configuration, when stored at controlled room temperature (20 °C to 25 °C, excursion permitted between 15 °C and 30 °C).

Conclusion: Drug product is acceptable.

Additional Items:

The analytical methods used for testing (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
6/27/2008 03:04:21 PM
CHEMIST

NDA 22-244

Aquavan®
(fospropofol disodium)
Injection

MGI Pharma, Inc.

Elsbeth Chikhale, Ph.D.
ONDQA – Division of Pre-Marketing Assessment I – Branch II
for
Division of Anesthesia, Analgesia and Rheumatology Products

Table of Contents

b(4)

Chemistry Review Data Sheet

1. NDA 22-244

2. REVIEW #: 1

3. REVIEW DATE: 27-JUN-2008

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	26-SEP-2007
Amendment to original[1]	15-NOV-2007
Amendment to original[2]	14-FEB-2008
Amendment to original[3]	26-FEB-2008
Amendment to original[4]	28-MAR-2008
Amendment to original[5]	6-JUN-2008

1) The 11/15/07 amendment provides for a response to a request from the Agency.
2) The 2/14/08 amendment provides for a response to the Agency's filing communication dated 12/14/2007.
3) The 2/26/08 amendment provides for a response to the Agency's request to withdraw the [redacted] contract facility. b(4)
4) The 3/28/08 amendment provides for updated drug product stability data.
5) The 6/6/08 amendment provides for a response to the Agency's information request dated 5/22/08.

7. NAME & ADDRESS OF APPLICANT:

Name: MGI Pharma, Inc.

Address: 6611 Tributary Street
Baltimore, MD 21224

Representative: Jacqueline M. Kline, Ph.D.

Telephone: (410) 631-5595

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Aquavan®
b) Non-Proprietary Name (USAN): Fospropofol disodium
c) Code Name/#: Chem. Type/Submission Priority:

- Chem. Type: 1 (new molecular entity)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: sedative-hypnotic agent

11. DOSAGE FORM: injection

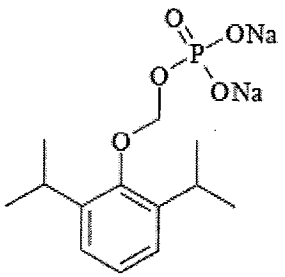
12. STRENGTH/POTENCY: 35 mg/mL

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
____SPOTS product ___ Form Completed
_x_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,MOLECULAR WEIGHT:



The molecular formula of fospropofol disodium is $C_{13}H_{19}O_5PNa_2$.
The molecular weight of fospropofol disodium is 332.24.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		4 & 7	N/A	N/A	DMF was used [redacted]

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no relevant revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (there is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	6/20/08	
Pharm/Tox	Approval	6/26/08	Mamata De, Ph.D.
Clinical Pharmacology	N/A		
Methods Validation	Acceptable	6/20/08	Elsbeth Chikhale, Ph.D.
ODS	Aquavan®	New trade name is pending	
EA	Acceptable	6/20/08	Elsbeth Chikhale, Ph.D.
Microbiology	Approval	6/16/08	John Metcalf, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 22-244

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-244 is **recommended for Approval (AP)** from the standpoint of chemistry, manufacture and controls. Final labeling will be done in coordination with the clinical division.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Product

The drug product, Aquavan® (fospropofol disodium) Injection, is a sterile, non-pyrogenic, iso-osmotic, clear, colorless, aqueous solution of fospropofol disodium intended for intravenous administration. The product is intended to be used as a sedative-hypnotic agent. It contains 35 mg/mL of fospropofol disodium, 0.25 % (w/w) monothioglycerol (MTG) [redacted] and 0.12 % (w/w) tromethamine (TRIS) [redacted] The formulation does not contain antimicrobial preservatives or any excipients of human and/or animal origin. Aquavan® is [redacted] at Baxter Pharmaceutical Solutions, LLC (Bloomington, IN). [redacted] b(4)

[redacted] The provided stability data support the proposed 36 month shelf-life when stored at controlled room temperature (25 °C, excursion permitted between 15 and 30 °C).

b(4)

2) Drug Substance

Fospropofol disodium (2,6-diisopropylphenoxymethyl phosphate, disodium salt) is a [redacted] solid that is a water soluble prodrug of propofol. It is converted to propofol in the body by the enzyme alkaline phosphatase. Propofol is the active ingredient of Diprivan® (propofol) Injection, 10 mg/mL, (NDA 19-627, approved in 1989). The drug substance, fospropofol disodium, is considered a new molecular entity (NME). It contains no chiral centers. Polymorphism was observed but not further investigated because in the aqueous dosage form the drug substance will be fully dissolved. The drug substance has pKa's of 1.19 and 6.27.

The molecular formula of fospropofol disodium is $C_{13}H_{19}O_5PNa_2$ and the molecular weight is 332.24. Fospropofol disodium is synthesized from propofol [redacted] Provided stability data support the proposed retest period [redacted] when stored at controlled room temperature. b(4)

B. Description of How the Drug Product is Intended to be Used

The drug product is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures. It is also [redacted] The standard dosing regimen is an initial IV bolus dose of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of the initial dose) as needed. No initial dose should exceed 16.5 mL; no supplemental dose should exceed 4 mL. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The NDA is **recommended for Approval (AP)** from chemistry, manufacturing and controls (CMC) perspective. CMC concerns are satisfactorily addressed; see below:

- The applicant has satisfactorily replied to the CMC information request dated 5/22/08.
- The CMC information for the drug substance, fospropofol disodium, is adequate
- The CMC information for the drug product is adequate.
- The proposed regulatory specifications for the drug substance are acceptable.
- The proposed in-process controls and regulatory drug product specifications are acceptable and assure a high quality drug product.
- Submitted stability data support the proposed expiry of **36 month** for the drug product when stored at controlled room temperature.
- The Microbiology review has recommended that the NDA be approved from a Microbiology standpoint

The labeling and labels of this application will be reviewed at a later time in coordination with the clinical division.

III. Administrative

A. Reviewer's Signature

Elsbeth Chikhale, Ph.D.

B. Endorsement Block: in DFS

C. cc Block: in DFS

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 5

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/s/

Elsbeth Chikhale
6/27/2008 02:53:22 PM
CHEMIST

Ali Al-Hakim
6/27/2008 03:00:34 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology
NDA:	22-244
Applicant:	MGI Pharma
Stamp date:	September 27, 2007
PDUFA Date:	July 27, 2008
Trademark:	Aquavan®
Established Name:	Fospropofol Disodium (USAN QQ-89)
Dosage Form:	Intravenous Injection (35 mg/ml)
Route of Administration:	Parenteral (IV)
Indication:	[redacted] b(4)
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(1), non-priority NDA with 10-month review clock, for the New Molecular Entity fospropofol disodium.

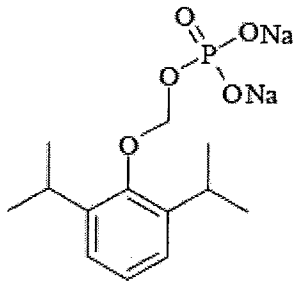
Fospropofol disodium is [redacted] water soluble. Fospropofol is a New Molecular entity (NME), according to the definitions in the FDA Drug Classification MAPP 7500-3. but not a "first in a class NME" since it is a prodrug of propofol (Diprivan® NDA 19-627, AP 1996). The drug substance is manufactured by [redacted] and, based on stability data provided by the sponsor, the drug substance is stable for [redacted] The drug product is formulated as a sterile solution,: therefore, particle size, morphic form and other solid properties of the drug substance are not expected to impact bioavailability of the drug. b(4)

AQUAVAN® (fospropofol disodium) Injection is a sterile, non-pyrogenic, iso-osmotic, clear, colorless, aqueous solution of fospropofol disodium for intravenous administration in conjunction with local anesthesia. AQUAVAN® contains 35 mg/mL of fospropofol disodium, 0.25 wt% monothioglycerol (MTG) [redacted] ; 0.12 wt% tromethamine (TRIS) as a [redacted] and no antimicrobial preservatives. The drug product is [redacted] manufactured at the [redacted] Baxter Pharmaceutical Solutions, LLC (Bloomington, IN). The product is [redacted] . Based on real time stability data, a 36 month shelf-life is proposed for AQUAVAN®. b(4)

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



1. 2,6-diisopropylphenoxymethyl phosphate, disodium salt
2. Methanol, [2,6-bis(1-methylethyl)phenoxy]-dihydrogen phosphate, disodium salt
3. [2,6-bis(1-methylethyl)phenoxy] methyl disodium phosphate

Molecular formula: $C_{13}H_{19}O_5PNa_2$
Molecular Weight: 332.24 g/mol

12 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 6

assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review. Even though the drug substance is an NME, the [redacted], the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development. In addition, the commercial AQUAVAN® process is representative of the pilot scale (clinical Phase 3) process. b(4)

Consults:
Since AQUAVAN® is an injectable product, microbiology consult is required and was initiated (Section 3.2.A.1)..
Specifications for impurities and structural alerts should be evaluated in consultation with the Toxicology reviewer.
The primary reviewer, in conjunction with the project manager, should initiate the following consults/requests as soon as possible (see fileability template below).

Danae D Christodoulou, Ph.D. — 11/6/2007
Pharmaceutical Assessment Lead — Date

Ali Al-Hakim, Ph.D. — 11/9/07
Branch II Chief — Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Injectable
16	Have all consults been identified and initiated?	√ √ √ √ N/A √		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LoA Included	Status
[redacted]				

b(4)

Supporting IND: 62,860

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/s/

Danae Christodoulou
11/9/2007 02:30:16 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
11/9/2007 02:34:53 PM
CHEMIST