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

- 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:

b(A)
Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry-4
LUSEDRA
fospropofol disodium injection

Product Information

Product Type: HUMAN PRESCRIPTION DRUG
Route of Administration: INTRAVENOUS

INGREDIENTS

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

Product Characteristics

Color
Shape
Flavor
Contains

Packaging

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

Evaluation: The SPL is acceptable.

Note:
There are no remaining CMC issues, therefore NDA 22-244 is recommended for APPROVAL from CMC perspective.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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.
661 1 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 and 0.12 % (w/w) TRIS pH 8.6. Each vial is sealed with

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_{3}PNa_{2}, a molecular weight of 332.24, and pKa's of 1.19 and 6.27. Known chemically as 2,6-diisopropylphenoxyethyl phosphate, disodium salt, it is a
and is freely soluble in water. It contains no chiral centers. Polymorphism was observed but not further investigated because the drug substance will be fully dissolved in the aqueous dosage form.

Adequate stability data were provided to support a retest date 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 and 0.12 % (w/w) TRIS USP pH 8.6.

Specification of the drug product includes: appearance, clarity, color, identification by
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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
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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:

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<td>Amendment to original$^5$</td>
<td>6-JUN-2008</td>
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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 contract facility.
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
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 ___ OTM

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:

![Chemical Structure]

The molecular formula of fospropofol disodium is C_{13}H_{19}O_{5}PNa_{2}.
The molecular weight of fospropofol disodium is 332.24.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
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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

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<th>DESCRIPTION</th>
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CHEMISTRY REVIEW
Chemistry Review Data Sheet

18. STATUS:

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<td>Mamata De, Ph.D.</td>
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<td>Elsbeth Chikhale, Ph.D.</td>
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<td>Elsbeth Chikhale, Ph.D.</td>
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<td>Elsbeth Chikhale, Ph.D.</td>
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<td>Elsbeth Chikhale, Ph.D.</td>
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<tr>
<td>Microbiology</td>
<td>Approval</td>
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<td>John Metcalf, Ph.D.</td>
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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) and 0.12 % (w/w) tromethamine (TRIS). The formulation does not contain antimicrobial preservatives or any excipients of human and/or animal origin. Aquavan® is manufactured by Baxter Pharmaceutical Solutions, LLC (Bloomington, IN).

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).

2) Drug Substance

Fospropofol disodium (2,6-diisopropylphenoxyethyl phosphate, disodium salt) is a 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$_5$PNa$_2$ and the molecular weight is 332.24. Fospropofol disodium is synthesized from propofol. Provided stability data support the proposed retest period when stored at controlled room temperature.

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

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.

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
Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
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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**

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<th>Anesthesia, Analgesia and Rheumatology</th>
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<td>NDA:</td>
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<tr>
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<td>MGI Pharma</td>
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<td>September 27, 2007</td>
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<td>July 27, 2008</td>
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<td>Indication:</td>
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Pharmaceutical Assessment Lead: Danae D. Christodoulou, Ph.D.

ONDQA Fileability: YES

Comments for 74-Day Letter: YES
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 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 and, based on stability data provided by the sponsor, the drug substance is stable for 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.

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), 0.12 wt% tromethamine (TRIS) as a and no antimicrobial preservatives. The drug product is manufactured at the Baxter Pharmaceutical Solutions, LLC (Bloomington, IN). The product is based on real time stability data, a 36 month shelf-life is proposed for AQUAVAN®.

B. Review, Comments and Recommendations
Drug Substance
Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

![Molecular Structure]

1. 2,6-diisopropylphenoxy methyl 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: C₁₃H₁₉O₅PNa₂
Molecular Weight: 332.24 g/mol
Page(s) Withheld

✓ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
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 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.

**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.  
Pharmaceutical Assessment Lead  
11/6/2007  
Date

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

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<td>2  Is the section indexed and paginated adequately?</td>
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<td>3  On its face, is the section legible?</td>
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<td>11 Have draft container labels been provided?</td>
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Have all DMF References been identified? Yes (✓) No (✗)

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Supporting IND: 62,860
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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