

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-244

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-244

SUPPL #

HFD # 170

Trade Name Lusedra

Generic Name fospropofol disodium

Applicant Name Eisai Medical Research

Approval Date, If Known December 12, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications; and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO." GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no." identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES
Explain:

!
!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: Allison Meyer
Title: Regulatory Health Project Manager
Date: June 12, 2008

Name of Office/Division Director signing form: Rigo Roca
Title: Deputy Director, HFD-170

Form OGD-011347: Revised 05/10/2004; formatted 2/15/05

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

/s/

Rigoberto Roca
12/12/2008 01:02:35 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-244 Supplement Number: NDA Supplement Type (e.g. SE5):

Division Name: DAARP PDUFA Goal Date: 12-12-08 Stamp Date: 9/26/07

Proprietary Name: Lusedra

Established/Generic Name: fospropofol disodium

Dosage Form: Injectable

Applicant/Sponsor: Eisai Medical Research

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: monitored anesthesia care sedation in patients undergoing therapeutic and diagnostic procedures

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed [‡]	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	0 yr. 0 mo.	3 yr. 0 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	3 yr. 1 mo.	17 yr. 0 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	0 yr. 0 mo.		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): 03/31/2012						

Are the indicated age ranges (above) based on weight (kg)? X No: Yes:

Are the indicated age ranges (above) based on Tanner Stage? X No: Yes:

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.
 Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so).

proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

Allison Meyer
12/10/2008 10:10:51 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-244 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: September 27, 2007 PDUFA Goal Date: July 27, 2008

HFD-170 _____ Trade and generic names/dosage form: Aquavan (fospropofol disodium) Injection

Applicant: MGI Pharma Therapeutic Class: IS

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DfS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. 0 Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment 1. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-244

Page 3

This page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

(See attached electronic signature page.)

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STATE at 301-796-0700

(Revised: 10/10/2006)

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/s/

Parinda Jani

1/7/2008 04:31:37 PM

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, December 04, 2008 2:31 PM
To: 'Jacqueline_Kline@eisai.com'
Subject: Pediatric dates

Jackie,

As a part of the Required Pediatric Assessments portion of the action letter, it is a requirement to include specific dates for the following 3 items, Protocol Submission, Study Start Date, and Final Report Submission. I will need these specific dates from you today for studies 1-4!

Thanks,
Allison

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, December 09, 2008 3:53 PM
To: 'Jacqueline_Kline@eisai.com'
Subject: FW: Labeling comments

Jackie,
Please address ASAP.

Cartons and containers: two remaining comments

Storage statement should read:.....Excursions permitted between 15 °C and 30 °C (59 °F and 86 °F).

- "Injection" in the name should be with a capital "I".

- Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

Allison Meyer
12/12/2008 09:21:27 AM
CSO

PREAPPROVAL SAFETY CONFERENCE

MEETING DATE: November 25, 2008
TIME: 2:00 to 3:30 pm
LOCATION: White Oak Campus, Bldg 22, Room 3270
TYPE OF MEETING: Pre-Approval Safety Conference

MEETING CHAIR: Rigoberto Roca, M.D.

MEETING RECORDER: Allison Meyer/Chris Wheeler

FDA ATTENDEES: (Title and Office/Division)

Division of Analgesia, Anesthesia, and Rheumatology Products

Rigoberto Roca, M.D.	Deputy Director
Bindi Nikhar, M.D.	Anesthesia Team Leader
Lex Schultheis, M.D. Ph.D.	Clinical Reviewer
Mitch Frost, M.D.	Clinical Reviewer
Dionne Price, M.D.	Biostatistics Team Leader
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Larissa Lapteva, M.D.	Associate Director of Safety
Ayanna Augustus, Ph.D.	Regulatory Project Manager
Allison Meyer	Regulatory Health Project Manager

Division of Pharmacovigilance

Bob Boucher, M.D.	Deputy Director
Peter Diak, Pharm.D.	Acting Team Leader

Office of Surveillance and Epidemiology

Chris Wheeler	Regulatory Project Manager
---------------	----------------------------

BACKGROUND: This NDA is an NME for the pro-drug of propofol. This is a Class 1 Resubmission, 2nd cycle review. Overall safety concerns are similar to propofol.

MEETING OBJECTIVES:

- Engage OSE and OND in discussion of possible safety concerns of fospropofol.
- Allow OSE opportunity to express any safety concerns not discussed by the review division
- Discuss how any potential safety concerns will be managed

DISCUSSION:

Relationship to propofol:

OND discussed the history of the application and the NA letter sent in the previous cycle. Fospropofol originally wanted labeling that permitted use without an anesthesiologist, although the safety profile is very similar to propofol. The application was given an NA until they adopted labeling similar to propofol. Possible safety issues could arise in the future if the applicant wishes to pursue alternative labeling.

Post-Market Studies:

The applicant will have post-marketing requirements upon approval. This is due to certain populations showing higher rates of adverse events that require airway intervention. These populations are typically lower weight patients, patients of an ASA class 3 or 4, and elderly patients (>65 years). The applicant will be asked to conduct studies exploring this risk. OSE asked if the review division wished to limit the use of fospropofol in these at risk populations until the PMRs were complete. The review division indicated that fospropofol was effective and well tolerated in the at risk groups for the most part, but they still wanted to explore it. The label does recommend dose adjustments for smaller and older patients.

Oral Bioavailability and Scheduling:

Fospropofol will be a Schedule IV product upon approval. The product is water soluble and therefore orally bioavailable. OSE mentioned the oral route could lead to potential abuse, however this risk is considered to be quite small.

ACTION ITEMS:

Post-Marketing Requirements pending SRT approval

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/s/

Allison Meyer
12/4/2008 04:23:43 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

DISCIPLINE REVIEW LETTER

Eisai Medical Research, Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

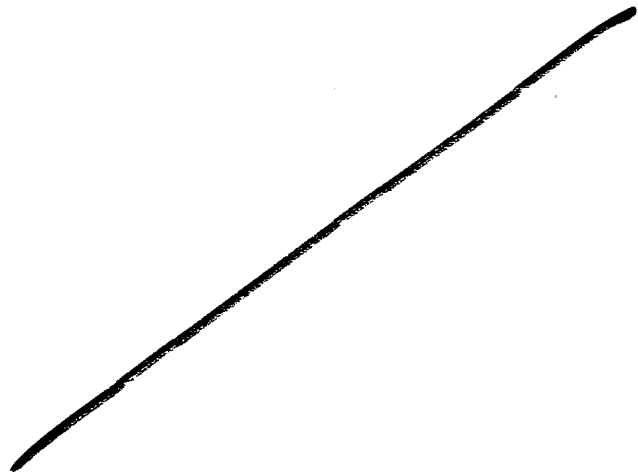
Attention: Jacqueline Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your October 13, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium injection.

The Division of Medication Error Prevention and Analysis review of the labeling section of your submission is complete, and we have identified the following deficiencies:

b(4)



b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
12/2/2008 01:01:43 PM

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

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE/DMEPA, White Oak Bldg. 22

FROM: HFD-170, Division of Anesthesia, Analgesia, and
Rheumatology Products

Allison Meyer

DATE
10/31/08

IND NO.

NDA NO.
22-244

TYPE OF DOCUMENT
Labeling

DATE OF DOCUMENT
10/13/08

NAME OF DRUG
Lusedra

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Anesthetic

DESIRED COMPLETION DATE
11/28/08

NAME OF FIRM: Eisai

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton and Container labeling |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV 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

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the carton and container labels and package insert for the NDA 22-244 from 10/13/08. This is an electronic submission. \\CDSESUB1\NONECTD\N22244\N 000\2008-10-13
If you have any questions, please contact Allison Meyer at 301-796-1258.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Allison Meyer
10/31/2008 11:44:57 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

Eisai Medical Research Inc.
55 Challenger Road
Ridgefield Park, NJ 07660

Attention: Jacqueline Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

We acknowledge receipt on October 14, 2008, of your October 13, 2008, resubmission to your new drug application for Lusedra (fospropofol disodium) Injection.

We consider this a complete, Class 1 response to our July 23, 2008, action letter. Therefore, the user fee goal date is December 14, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

If you have any question, call me, at (301)796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer

10/29/2008 01:01:22 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-244

Eisai Medical Research Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium.

We also refer to the meeting between representatives of your firm and the FDA on September 8, 2008. The purpose of the meeting was to discuss the deficiencies indentified in the Not Approvable letter dated July 23, 2008.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 8, 2008
TIME: 2:00-3:00 pm (EST)
LOCATION: White Oak, Bldg 22, Rm 1313
APPLICATION: NDA 22-244
DRUG NAME: fospropofol disodium
TYPE OF MEETING: Type A meeting

MEETING CHAIR: Rigoberto Roca, M.D., Deputy Division Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)


MEETING RECORDER: Allison Meyer, Regulatory Health Project Manager

FDA ATTENDEES: (Title and Office/Division)

FDA Attendees	Title
Curtis Rosebraugh, MD	Director, Office of Drug Evaluation II (ODE II)
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Bindi Nikhar, MD	Clinical Team Leader
Lex Schultheis, MD, PhD	Medical Officer
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Mary Dempsey	Regulatory Project Manager, OSE
Corinne Moody	Regulatory Project Manager, CSS
Ayanna Augustus	Regulatory Project Manager
Allison Meyer	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Sponsor Attendees	Title
Mary Lynne Hedley, PhD	Executive Vice President and CSO
Timothy Hsu, MD	Associate VP, Global Therapeutic Head, CNS I
Jacqueline Kline, PhD	Director, Regulatory Affairs
Lynn Kramer, MD, F.A.A.N	Executive Vice President, Clinical
Stacie O'Sullivan	Manager, Regulatory Affairs
Andrew Satlin, MD	Senior Vice President, CNS and Anti-Infectives

Ilona Surick, MD, MPH	Executive Director, International Pharmacovigilance
Mark Taisey	Vice President, Regulatory Affairs
Masanori Tsuno	President, Eisai Global Clinical
	

b(4)


BACKGROUND:

The purpose of the meeting was to discuss the deficiencies identified in the Not Approvable letter for NDA 22-244, fospropofol, dated July 23, 2008 and to discuss the planned resubmission of this application.

The Sponsor's questions are presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font.

Agency Comments and Responses to Questions:


Question 1:

...In combination with additional warning that deep sedation may occur, therefore, would  the use of fospropofol by anesthesiologist, critical care specialist, or pulmonologist be acceptable?

b(4)

FDA Response



A principal concern is that some patients became unresponsive or minimally responsive following administration of fospropofol. The risks associated with unresponsiveness associated with fospropofol are believed to be indistinguishable from those of a general anesthetic.  training in general anesthesia is required unless you can show that unresponsiveness caused by fospropofol is preventable or has a lower risk than general anesthesia.

b(4)

Discussion:

Following introductions, the Sponsor stated their intent to resubmit their application, which will include an amended package insert with information specifying administration by persons trained in general anesthesiology. The Sponsor intends to work with the package insert that was sent to them by the Division during the first cycle review and will include language for MAC sedation. The Sponsor requested classification of the resubmission as Class 1 resubmission subject to a two-month review clock. The Sponsor also requested clarification on the requirement of a REMS.

The Division stated that if the labeling for fospropofol is similar to the approved label for propofol, then a REMS may not be required, although new FDAAA considerations might require

a REMS. Therefore, further internal discussion was necessary before final recommendations could be given to the sponsor

Post-Meeting Note: If the Sponsor uses same labeling as propofol in regard to specifying administration by persons trained in general anestheiology, they will not need a REMS.

Question 2:

The action letter noted that the Sponsor could "provide additional and substantial evidence of fospropofol safety when used routinely by representative health care providers in their usual practice setting." The Sponsor believes that a study conducted by gastroenterologists in various practice settings, e.g., hospital, ambulatory surgi-center, and office based practice, would meet the definition of "representative health care providers."

Does the Division concur?

FDA Response

Although gastroenterologists and gastroenterology patients may comprise a significant component of the study, the study should also include providers from other specialties and patients with more severe and acute cardiopulmonary disease in order to adequately represent the expected exposure.

Discussion:

The Sponsor wanted to know whether studies conducted by gastroenterologists in patients undergoing procedures in various practice settings would be sufficient to support label expansion for a restricted patient population. The Division believes fospropofol will be used off-label, and therefore, its use should be evaluated in patient/practitioners populations other than gastroenterologists/gastroenterology patients. The Division stated that doses utilized during bronchoscopy provide a good starting point, but the Sponsor should consider evaluating the safety of fospropofol in cardiovascular patients undergoing catheterization procedures. The Division stated that an actual use study that assesses a training program for physicians and evaluates how practitioners use fospropofol may be the best approach. A randomized, blinded clinical trial with inferential statistics would not be appropriate for assessing the safety of fospropofol. The Sponsor may want to consider discussing their study design with the Division before starting additional Phase 3 trials. The Sponsor agreed to provide safety data from a more diverse group of patients/practitioners and plans to provide clear language in the product label that states that an anesthesiologist should be present and follow-up care should be provided along with proper marketing and communication to ensure proper use of fospropofol.

Question 3:

If additional studies conducted by representative health care providers in their usual practice settings result in similar rates of sedation related adverse events, interventions, and outcomes as was observed in the phase 3 program, the Sponsor believes this would constitute substantial evidence of fospropofol safety in the hands of these health care providers.

Does the Division concur?

FDA Response

No. While we agree that a safety study should be conducted by representative health care providers in their usual practice setting, substantial evidence of safety will require more than documentation that the incidence of adverse events is similar to the rate previously reported in Phase 3 studies. A design is needed that will enable a direct comparison between the adverse events associated with a standard-of-care sedation regimen and fospropofol.

The following safety concerns will also need to be addressed including:

- **Additional dose-ranging information is needed in geriatric patients, patients categorized as ASA 3 or 4, especially those with cardiopulmonary morbidities, and in patients weighing less than 60 kg because these groups appeared to exhibit an increased risk of hypoxia with the recommended dosing.**
- **Any proposal including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use as described under 505-1(e) of the Food and Drug Administration Amendments Act (FDAAA) should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS). However, a complete review of your Complete Response (CR) will be necessary to determine whether a REMS is needed to ensure that the benefits of the drug outweigh the risks and what components will be essential to assure safe use.**

You need to propose a training program to teach health care providers to assess patients who are at an increased risk of becoming unresponsive from fospropofol exposure and how to manage these patients safely.

For information on the format and content of a REMS, we refer you to the approval letter for Entereg (available at <http://www.fda.gov/cder/foi/label/2008/021775REMS.pdf>).

Remember to submit all planned materials identified within the proposed REMS that will be necessary to implement your proposal. Education should emphasize the safety messages important for safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

- **Any increment in the incidence of hypoxia associated with fospropofol compared with a standard-of-care sedation regimen will be interpreted as an unsafe trend. Hypoxia associated with fospropofol is likely to be a consequence of protracted hypoventilation. Therefore, monitoring systemic carbon dioxide as an indicator of ventilation may be able to preempt hypoxia and improve the safety of fospropofol.**

It is very likely that the results of the study will be taken to the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) for their input.

Discussion:

The Sponsor expressed confusion regarding what is needed to demonstrate that the safety profile for fospropofol is comparable to the safety profile of currently approved sedation drugs, because any increase in the incidence of hypoxia in fospropofol treated patients compared to midazolam treated patients would be seen as unsafe. The Division stated that data generated from an actual use study, including evaluation of an education/training program, could demonstrate the safety of fospropofol compared to currently approved sedation drugs for sedation-related adverse events. Furthermore, labeling fospropofol for sedation by health care providers who are not trained in general anesthesia is a paradigm shift that will require full public presentation of new data and safety outcomes at an Advisory Committee meeting.

The Sponsor requested advice on which markers or adverse events should be considered when evaluating the safety of fospropofol. The Division stated that the Sponsor should consider implementing the recommendations given during the Advisory Committee meeting, including monitoring of systemic carbon dioxide during Phase 3 studies. Systemic carbon dioxide levels are inversely proportional to minute ventilation and may be an early indicator of excessive sedation. The Division stated early signs of excessive sedation may enable detection of patients on fospropofol who eventually become hypoxic and/or become unresponsive. The Division stated that even without hypoxia, unresponsiveness will be regarded as unsafe because it carries the potential for aspiration or airway obstruction.

Monitoring systemic carbon dioxide to predict hypoxia in fospropofol treated patients may be an improvement in safety monitoring over standard-of-care safety monitoring in existing sedation practices. The Sponsor should consider exploring the benefits of such carbon dioxide monitoring in patients receiving fospropofol compared to standard-of-care monitoring of patients receiving alternative sedation products that do not require training in general anesthesia.

Question 4:

The action letter notes that the endpoints of a clinical study should include assessments to objectively evaluate the success of clinical training to providers of fospropofol sedation. The Sponsor believes that such assessments could include a survey to test providers' knowledge of fospropofol as well as clinical outcomes.

Does the Division concur?

FDA Response

A survey may be included, but will not constitute adequate testing by itself. The most compelling evidence used to evaluate successfulness of the clinical training program will be an analysis of adverse events.

However, serious adverse events are expected to occur infrequently so practical examination of sedation management skills should also be part of an ongoing training program to enable health care providers to maintain a high level of preparedness.

Discussion: No discussion necessary.

Question 5:

The Sponsor believes that safety could be evaluated in a clinical trial using measures that would include severity of, interventions for, and outcome of sedation related adverse events and serious sedation related events.

Does the Division concur?

Discussion: No discussion necessary

FDA Response

Yes, provided the analysis will provide comparative information relative to a standard-of-care-regimen with an approved product. In addition, the other safety concerns described in the answer to Question 3 will have to be addressed.

Question 6:

...Therefore, the Sponsor believes that demonstration that non-anesthesiology health care providers who are properly trained and qualified can independently and appropriately manage sedation-related events, irrespective of a patient's level of responsiveness, would constitute substantial evidence of fospropofol safety.

Does the Division concur?

FDA Response

No. A patient who is unresponsive from sedation may be difficult to differentiate from a patient who is under general anesthesia. Unless you can provide evidence to discriminate the risk to a patient who is unresponsive from fospropofol from the risk to a patient who is unresponsive from a general anesthetic, it may not be possible to demonstrate that skills in general anesthesia are not required to manage sedation of patients with fospropofol.

Discussion: No discussion necessary

Question 7:

The Sponsor believes that a "use" study, often described as a "large and simple" study, where only essential data supporting a measure of safety as a primary endpoint would be sufficient to provide additional and substantial evidence as requested by the Agency.

Does the Division concur?

FDA Response

In theory, this may be sufficient. However, since these data cannot be analyzed with inferential statistics, any increment in the incidence of adverse events associated with the fospropofol treatment group, compared to the standard-of-care treatment group, may be interpreted as evidence of as an unsafe trend within the fospropofol treatment group and will need to be addressed. The additional safety concerns described in the answer to Question 3 should also be addressed. As noted above, the study results will probably be presented at an ALSDAC meeting.

Discussion: See discussion for Question 3.

Sponsor Summary:

The primary aspect of the Sponsor's complete response will include an amended package insert which will contain new information that addresses the deficiencies in the Not Approvable letter and information obtained from the responses to questions submitted in the meeting package. The Sponsor planned to submit their complete response within two to three weeks. The Division suggested that the Sponsor submit their complete response only after the Division has had time to determine if the product will require a REMS. The Division also agreed to conduct a preliminary review of the amended product label prior to submission of a complete response package.

Action Items:

1. The Sponsor will submit a propofol-like label.
2. The Sponsor will submit a proposal for a label expansion (End-of-Phase 2, meeting request).

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/s/

Allison Meyer
9/30/2008 10:22:13 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

Eisai Medical Research Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium.

Attached are the Division's responses to the questions from your August 7, 2008, meeting package for our upcoming meeting, scheduled for September 8, 2008, to discuss issues related to the Not Approvable letter.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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/s/

Parinda Jani
9/5/2008 05:59:50 PM
CSO
for Allison Meyer



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

Eisia Medical Research Inc.
55 Challenger Road
Ridgefield Park, New Jersey 07660

Attention: Jacqueline M. Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium injection.

We also refer to your August 7, 2008, correspondence, received August 8, 2008, requesting a post-action meeting.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: September 9, 2008
Time: 1:00 pm
Location: White Oak, Bldg. 22
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDER participants: Curtis Rosebraugh, M.D., Ph.D.; Director, ODE II
Bob A. Rappaport, M.D.; Director
Rigoberto Roca, M.D.; Deputy Director
Bindi Nikhar, M.D.; Team Leader, Anesthesia
Lex Schultheis, M.D., Ph.D.; Medical Reviewer
Dan Mellon, Ph.D.; Supervisor, Pharmacology/Toxicology
Mamata De, Ph.D., Pharmacology/Toxicology Reviewer
Dionne Price, Ph.D.; Team Leader, Biometrics
Kate Meaker, Ph.D.; Biometrics Reviewer
Suresh Doddapaneni, Ph.D.; Team Leader, Biopharmaceutics
Sirkanth Nallani, Ph.D.; Biopharmaceutics Reviewer
Ali Al Hakim, Ph.D.; Branch Chief, CMC
Elsbeth Chikhale, Ph.D.; CMC Reviewer
Allison Meyer; Regulatory Project Manager
Ayanna Augutus, Ph.D.; Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Allison.Meyer@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Allison Meyer, x 1258; the division secretary, x 2280.

Provide the background information for this meeting (three copies to the NDA and 17 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by August 25, 2008, we may cancel or reschedule the meeting.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer
8/14/2008 09:56:33 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

NOT APPROVABLE

MGI Pharma, Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your new drug application (NDA) dated September 26, 2007, received September 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium Injection.

We acknowledge receipt of your submissions dated November 5, 7, 16, and 30, 2007, and January 3, February 15, 26, and 29, March 6, 21, and 28, April 7 and 15, May 15, 21, and 30, and June 6 and 27, 2008.

We also acknowledge receipt of your submissions dated June 9, 13, and 27 and July 3, 2008. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

CLINICAL

You have not provided adequate information to support your proposal that providers can safely manage sedation of patients with fospropofol. Although adequate evidence of efficacy was demonstrated, some subjects experienced undesired deep sedation resembling general anesthesia and/or hypoxia associated with fospropofol.

b(4)

Information Required to Address Deficiencies:

b(4)

b(4)

anesthesia, so your label should state that fospropofol should be administered only by health care providers trained in the administration of general anesthesia and not involved in the conduct of the procedure.

Alternatively, you can provide additional and substantial evidence of fospropofol safety when used routinely by representative health care providers in their usual practice setting. This evidence should be derived from a clinical study that is representative of the patient population likely to be exposed in practice. The health care providers who participate in this study should be trained via a protocol that will be available to all potential users and will provide substantial training that will allow practitioners to independently manage all clinical scenarios associated with fospropofol administration. Assessments to objectively evaluate the success of this clinical training to providers of fospropofol sedation should be incorporated into the endpoints of the clinical study.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Anesthesia, Analgesia, and Rheumatology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
7/23/2008 04:57:28 PM

MEMORANDUM OF TELECON

DATE: July 8, 2008

APPLICATION NUMBER: NDA 22-244

BETWEEN:

Name: Jackie Kline, Ph.D., Director Regulatory Affairs
Stacie O'Sullivan, Manager Regulatory Affairs
Ilona Surick, MD, MPH, Executive Director, International Pharmacovigilance
Mark Taisey, Vice President Regulatory Affairs

b(4)

Phone: 866-321-0153

Representing: MGI Pharma

AND

Name: Dr. Curt Rosebraugh
Dr. Rigo Roca
Dr. Bindi Nikhar
Dr. Lex Schultheis
Dr. Thomas Permutt
Dr. Srikanth Nallani
Ms. Leah Ripper
Ms. Parinda Jani
Ms. Allison Meyer
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

SUBJECT: labeling and REMS

During this teleconference, the Division informed the Sponsor that the language in the fospropofol label would need to be similar to the approved propofol labeling with regard to administration and use only to anesthesia trained individuals. This decision was made after review of the application and recommendations of members of the Advisory Committee, from the meeting held on May 7, 2008. Alternate wording for the label may be possible in the future if an adequate REMS or further study by the Sponsor prove safe use for a broader range of physicians. The Sponsor was unwilling to accept anesthesiologist only use wording in the label and therefore it was deemed that the two parties were at an impasse. Acceptable language could not be agreed upon.

Dr. Rosebraugh informed the sponsor that upon cursory review, the current REMs submission would not be adequate; however a comprehensive review had not been complete and would not be done during this review cycle. An untested REMS, prior to approval would require a pre-approval study.

The Sponsor was informed that there would be several other sections of the label that would need negotiation, including pharmacology/toxicology, clinical pharmacology, and clinical trials. These negotiations will be part of a future teleconference.

Allison Meyer
Regulatory Project Manager

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/s/

Allison Meyer
7/15/2008 11:07:57 AM
CSO

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: FW: Information Request
Date: Wednesday, June 04, 2008 1:07:57 PM
Attachments:

Jackie,
Please respond by Friday.

Submit the Fospropofol and propofol PK parameters for all the hepatic impaired in the following format.
Fospropofol Individual PK Parameters for patients with hepatic impairment as estimated by Model 120

Unique

Subject #	Child-Pugh Class	CL_F (L/min)	t_{1/2term}^F (min)	AUC_∞^b (mcg*hr/mL)
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365-0001
0524-
544-0003
0523-
559-0002
0523-
565-0016

0523-
561-0001
0523-
565-0023
0523-
565-0025

Propofol Individual PK Parameters for patients with hepatic impairment as estimated by Model 120

Unique

Subject # Child-Pugh Class CL_F

(L/min) t_{1/2term}^F

(min)^b AUC_∞

(mcg*hr/mL)

0524-

544-0003
0523-
559-0002
0523-
565-0016
0523-
561-0001

0523-
565-0025

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3189
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

Allison Meyer
7/9/2008 04:22:02 PM
CSO

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: NDA 22-244 information request chemistry
Date: Thursday, May 22, 2008 11:26:46 AM
Attachments:

Jackie,
Please respond ASAP, thanks Allison

Drug Substance:

- *Provide a UV spectrum for the drug substance, fospropofol disodium.*
- *Provide available stability data for the primary drug substance batches (manufactured at. _____) b(4)*
- *In accordance to ICH Q3A, qualify the _____ impurity or tighten the drug substance specification's acceptance criteria for _____ to NMT _____ b(4)*

Drug Product:

- *Provide a CFR reference for the _____ drug product stopper material. b(4)*
- *Provide a stability commitment containing wording similar to:*

_____ b(4)

- *In your amendment dated 2/26/08, a revised list of manufacturing facilities was provided, reflecting the removal of _____ as a contract laboratory. However, the list should be revised again, to reflect the correct name and address of _____*

b(4)

Appears This Way
On Original

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: FW: Today's Teleconference
Date: Thursday, April 24, 2008 1:41:40 PM
Attachments:

Please find our request below:

"Please present information on how the current proposed dosing regimen is better than a fixed mg/kg dosing regimen in the three weight groups (<60 kg, 60-90 kg and >90 kg) in terms of the distribution of plasma concentrations of fospropofol and propofol across time.

We would like you to present

- (A) Actual observed concentrations in clinical studies
- (B) Relationship between PK parameters and bodyweight
- (C) Model based simulated concentrations for the three weight groups in scenarios comparing the dosing regimens.

-----Original Message-----

From: Kline, Jacqueline [<mailto:Jacqueline.Kline@mgipharma.com>]
Sent: Thursday, April 24, 2008 11:32 AM
To: Meyer, Allison
Subject: Today's Teleconference

Allison,

Thank you for setting up the teleconference with us today. We really appreciated the opportunity to speak with you.

We want to ensure we include the information that your Clinical Pharmacologist mentioned. To that end, can you please shoot me an e-mail that describes exactly what he would like for us to include?

Thanks,
Jackie



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-244

DISCIPLINE REVIEW LETTER

MGI Pharma
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline Kline, PhD
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your September 26, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fospropofol disodium injection.

The Controlled Substance Staff (CSS) has reviewed the Abuse Liability Assessment (Module 5.3.5.4) as well as supporting studies and data and have identified the following deficiencies:

The data available demonstrate that fospropofol is soluble in water _____ is orally bioavailable, and produces sedative and euphoric effects from enteral (either oral or duodenal) administration. Propofol, the active metabolite of fospropofol, produces sedative and euphoric effects, is misused and abused, and has been associated with the death of persons misusing or abusing it. Therefore, CSS has concluded that fospropofol has a higher abuse potential than that of propofol because fospropofol is orally bioavailable.

b(4)

Additionally, the potential use of fospropofol in the context of criminal activity for the purpose of incapacitating a victim is of concern. Other orally active sedative agents such as GHB have been associated with criminal activity. In addition, if fospropofol is ingested with alcohol a potentiation of the sedative and depressant effects of fospropofol is expected.

Fospropofol has a pharmacological profile similar to sedatives scheduled under the Controlled Substance Act (CSA), pentobarbital (Schedule II) and GHB (Schedule I). Thus, fospropofol, like pentobarbital, and GHB, has a high potential for abuse and its abuse may lead to severe psychological or physical dependence and should be placed under Schedule II of the CSA.

Therefore, CSS recommends that fospropofol be scheduled under the Controlled Substances Act (CSA). CSS reminds you that fospropofol can not be marketed once approved until the scheduling action is complete. The scheduling process requires an eight-factor analysis and approval of the FDA Commissioner and HHS (Assistant Secretary for Health) prior to DEA notice of proposed rulemaking and final action.

You should reevaluate all data available on fospropofol, taking into consideration the conclusions of the CSS, and accordingly submit a proposal for placing fospropofol under Schedule II of the CSA.

If you propose a different Schedule than Schedule II, you will have to conduct studies to support the proposal. The following studies will be required:

1. Studies to characterize the binding profile of fospropofol should be repeated using validated experimental procedures.
2. Studies evaluating the bioavailability of fospropofol, oral and intravenous, should be repeated using only the liquid formulation (as to be marketed). Although fospropofol can be further metabolized to propofol *in vitro* use of sodium orthovanadate (an inhibitor of alkaline-phosphatase) in the studies examining the abuse liability of oral administration of fospropofol is not recommended because of the effects on the stability of propofol. The measurement of either fospropofol or propofol after the oral administration of fospropofol is sufficient to demonstrate oral bioavailability. An arm examining the oral bioavailability of propofol is recommended.

The protocol for these studies should include assessments for adverse events and drug effects, and evaluations for sedation.

3. Clinical studies examining the abuse potential oral fospropofol should be performed. In order to fully characterize the abuse potential of fospropofol, the drug should be compared to other CNS depressants that are controlled under the CSA as well as to propofol. Additionally, the effect of fospropofol in combination with ethanol should be examined as it may increase the abuse potential of fospropofol and might result in death.

CSS will be available to review the submitted eight factor analysis or protocols examining the abuse potential of intravenous and oral fospropofol and to discuss these issues you.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
4/22/2008 04:27:06 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: April, 2008

TO: Allison Meyer, Regulatory Project Manager
Dr. Lux Schultheis, Medical Officer

FROM: Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-244

APPLICANT: MGI Pharma, Inc.

DRUG: Aquavan® (fospropofol disodium)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Sedation

CONSULTATION REQUEST DATE: November 15, 2007

DIVISION ACTION GOAL DATE: July 23, 2008

PDUFA DATE: July 25, 2008

I. BACKGROUND:

Aquavan is a new molecular entity. The sponsor, MGI Pharma, Inc. has submitted a new drug application for marketing approval of Aquavan for sedation. Unexpectedly few serious adverse events were reported for study 3000-0522. Drs. Gregory Feldman (3000-

0524), Allan Seibert (3000-0524), Atul Shah (3000-0522), Gerard Silvestri (3000-0524), and C. Allen Goetsch (3000-0522) were selected for inspection due to enrollment of a large number of subjects at their sites. In addition, there was a large difference in frequency of serious adverse events reported at Drs. Gregory Feldman's, Allan Seibert's, and Gerard Silvestri's sites. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The protocols inspected include:

- **3000-0522** entitled "A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy"
- **3000-0524** entitled "A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy"

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Protocol #	Inspection Date	Final Classification
Gregory Feldman, M.D., Site 540 S. Carolina Pharmaceutical Research 1330 Boiling Springs Road, Suite 2100 Spartanburg, SC 29303	Protocol 3000-0524	February 04- 08, 2008	NAI
Gerard Silvestri, M.D., Site 544 Medical University of South Carolina Division of Pulmonary/Critical Care Medicine 96 Jonathan Lucas Street, CSB-812 Charleston, SC 29425	Protocol 3000-0524	January 22- 30, 2008	NAI
Atul Shah, M.D., Site 518 Shah Associates 110 Hospital Drive, Suite 303 Prince Frederick, MD 20678	Protocol 3000-0522	January 28- February 7, 2008	VAI
C. Allen Goetsch, M.D., Site 303 Clinical Research Associates, LLC 131 Longwood Drive Huntsville, AL 35801	Protocol 3000-0522	February 20- 21, 2008	NAI
Allan Seibert, M.D., Site 321 Pulmonary Associates of Mobile, P.C. 6701 Airport Boulevard, Suite B-135 Mobile, AL 36608	Protocol 3000-0524	February 11- 14, 2008	NAI
MGI Pharma, Inc. 6611 Tributary Street Baltimore, MD 21224	Protocol 3000-0522 Protocol 3000-0524	February 5-8, 2008	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Gregory Feldman, M.D., Site 540
S. Carolina Pharmaceutical Research
1330 Boiling Springs Road, Suite 2100
Spartanburg, SC 29303
 - a. **What was inspected:** For protocol 3000-0524, 41 subjects were screened, of which 33 subjects were randomized and completed the study. Informed consent documents for all subjects were reviewed. An audit of 22 subjects' records was conducted.
 - b. **General observations/commentary:** No significant regulatory violations were noted.
 - c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

2. Gerard Silvestri, M.D., Site 544
Medical University of South Carolina
Division of Pulmonary/Critical Care Medicine
96 Jonathan Lucas Street
Charleston, SC 29425
 - a. **What was inspected:** For protocol 3000-0524, 29 subjects were screened, of which 27 subjects were enrolled and completed the study. Informed consent documents for all subjects were reviewed. An audit of 18 subjects' records was conducted.
 - b. **General observations/commentary:** No significant regulatory violations were noted.
 - c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

3. Atul Shah, M.D., Site 518
Shah Associates
110 Hospital Drive, Suite 303
Prince Frederick, MD 20678

- a. **What was inspected:** For protocol 3000-0522, 33 subjects were screened; 30 subjects were randomized and completed the study. An audit of 10 subjects' records was conducted.
 - b. **General observations/commentary:** The inspection revealed protocol violations regarding dosage of study medications administered to subjects 0004 and 0028. Specifically:
 - The protocol specified that the initial bolus for subjects in the Midazolam group should be 0.02 mg/kg. The corresponding dosing guidance table indicates that for subjects whose weights are greater than 90 kg the dose will need to be calculated based on the subject's weight. Subject 0004 weighed 95 kg, but was administered the maximum dosage of 2.5 mg in violation of the protocol.
 - The protocol specified that subjects who are 65 years of age or older or who are classified as ASA P4 will receive initial and supplemental doses that are reduced by 25% from the randomized dose. Subject 0028, was over 65 years old but did not receive the protocol required initial and supplemental doses that are reduced by 25% from the randomized dose.
 - c. **Assessment of data integrity:** Data from this site appear acceptable in support of the pending application.
4. C. Allen Goetsch, M.D., Site 303
Clinical Research Associates, LLC
131 Longwood Drive
Huntsville, AL 35801
- a. **What was inspected:** For protocol 3000-0522, 31 subjects were screened; 30 subjects were randomized and completed the study. An audit of all subjects' records was conducted.
 - b. **General observations/commentary:** No significant regulatory violations were noted.
 - c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.
5. Allan Seibert, M.D., Site 321
Pulmonary Associates of Mobile, P.C.
6701 Airport Boulevard, Suite B-135
Mobile, AL 36608
- a. **What was inspected:** For protocol 3000-0524, 39 subjects were screened and 35 subjects were enrolled. An audit of all subjects' records was conducted.

- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

6 MGI Pharma, Inc.
6611 Tributary Street
Baltimore, MD 21224

- a. **What was inspected:** The inspection audited protocols 3000-0522 (sites 348, 368, 517, 518, 303, and 526) and 3000-0524 (Sites 321, 540, 544, 555, and 566). The inspection included review of standard operating procedures and monitoring reports.
- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data for this sponsor appear acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above, inspection of Dr. Shah found protocol violations. The inspection of the other sites found no significant regulatory violations. Data generated from each study site, and monitored by the sponsor, appear acceptable in support of the pending application.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Sherbert Samuels
4/21/2008 12:29:55 PM
CSO

Constance Lewin
4/21/2008 03:49:32 PM
MEDICAL OFFICER

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: FW: Clin Pharm Information Request for Aquavan
Date: Tuesday, April 01, 2008 11:30:05 AM
Attachments:

Jackie,

"Please submit information similar to Table 18 in Summary of Clinical Pharmacology Studies using data from all the studies. The current table in Summary of Clinical Pharmacology studies has information only from Study 3000-0522 and 3000-0524. We need information from all studies on change from baseline observed MOAA/S scores by age, albumin, ASA status etc as currently shown in Table 18"

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3189
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: Info request micro
Date: Thursday, March 20, 2008 12:29:58 PM
Attachments:

Provide the following information:

- It is stated in Module 3.2.A.1.5.3 of the NDA that _____
_____ have not yet been determined and that these
limits will be established based on data obtained through
process validation. Have these studies been performed?
Provide the _____ for the following time
periods:

b(4)

- _____
- _____

b(4)

- _____
qualification data demonstrating the suitability of use of this
test method with the subject drug product _____

b(4)

Thank you,
Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3189

Silver Spring, MD 20993

301-796-1258

301-796-9713 (fax)

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: tradenames
Date: Monday, March 10, 2008 3:51:35 PM
Attachments:

Jackie,
Please send me additional choices for tradenames for Aquavan.
Allison

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: aquavan non-clinical
Date: Friday, February 15, 2008 10:48:44 AM
Attachments:

Jackie,

Send the historical control data from the following non clinical studies:

1. Rat data from the Segment I and Segment III reproductive toxicity studies;
2. Rat and Rabbit data from the Segment II reproductive toxicity studies.

Thanks,
Allison J. Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301)796-1258
10903 New Hampshire Avenue
Building 22, Room # 3189
Silver Spring, MD 20993

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: Comments to Aquavan
Date: Wednesday, February 06, 2008 8:54:17 AM
Attachments:

Jackie: Please address, asap. Also, please update me as to the status of answering the requests in the 74-day letter.

Allison

Your primary endpoint is QTcI, which was computed using the 11 time points extracted from the continuous digital recorder at baseline. Based upon visual inspection of the trends in individual's QTcI and RR intervals, the individual correction method you used did not sufficiently correct for heart rate. The range of baseline heart rates from the 11 time points extracted from the continuous digital data was too narrow to compute an individual heart rate correction to account for the increase in heart rate with Aquavan administration.

To obtain better precision of the effects of administering Aquavan on the QT interval, you may want to reanalyze the data using an individual corrected QT interval computed from the 24-hour data (if available) obtained at baseline. Using the 24-h data will allow for the characterization of individual's QT-RR relationship over a larger range of heart rates. The effect of hysteresis between the QT-RR intervals should be assessed.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-244

MGI Pharma, Inc.
6611 Tributary Street
Baltimore, MD 21224-6515

Attention: Jacqueline Kline, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kline:

Please refer to your new drug application (NDA) dated September 26, 2007, received September 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for AQUAVAN™ (fospropofol disodium) Injection.

We also refer to your submissions dated November 5, 7, 16 and 30, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 26, 2008.

During our filing review of your application, we have identified the following potential review issues:

1. It is indicated in the submission that after being liberated from fospropofol disodium, propofol undergoes further biotransformation as described in the following references (*Simons, 1988, Gray, 1992*). It is also mentioned that fospropofol does not induce or inhibit CYP enzymes based on results from a 14-day IV infusion toxicity study (3000-15715-00-06G) in dogs.

Provide information about the specific metabolic pathways (e.g., CYP or non-CYP) of propofol clearance. Provide information on the potential for fospropofol and propofol to induce or inhibit major CYP enzymes. If this information is provided within the submission indicate the location of the information.

Preferred tools for assessing drug interaction potential with regard to CYP enzyme inhibition and induction are indicated in the Draft guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>).

2. Provide a summary table containing the drug lot numbers, purity, and composition of drug product tested in the toxicity studies.
3. Provide safety information for the identified leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the intravenous route of administration. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). Include copies of all referenced literature.
4. Amend 9-, 12- and 18-month stability data and updated stability summaries for the AQUAVAN supporting batch 904152 manufactured at Baxter.
5. According to the Physicians Labeling Rule, the package insert must be changed to **Bold** the Adverse Reactions and Patient Counseling Information Statement in Section I: Overview of Highlights. Also, in Section IV: Overview of Full Prescribing Information, the periods need to be removed after the numbers for the section or subsection headings.
6. As per your email dated November 30, 2007, the indication has been revised to "AQUAVAN® (fospropofol disodium) Injection is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures," and should be reflected in the package insert once labeling negotiations have commenced.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for

a deferral of pediatric studies for this application for all pediatric patients including neonates, infants, children and adolescents.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
12/14/2007 10:21:01 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-244 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Aquavan
Established Name: fospropofol disodium
Strengths: 35 mg/mL

Applicant: MGI Pharma, Inc.
Agent for Applicant (if applicable):

Date of Application: 9/26/07
Date of Receipt: 9/26/07
Date clock started after UN:
Date of Filing Meeting: 11/9/07
Filing Date: 11/25/07
Action Goal Date (optional):

User Fee Goal Date: 7/26/08

Indication(s) requested: intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures

Type of Original NDA: (b)(1) (b)(2)
 AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
 Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: 5 year exclusivity for NME

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fn1.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 62,860
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s) Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/9/07

NDA #: 22-244

DRUG NAMES: Aquavan

APPLICANT: MGI

BACKGROUND: This NDA is an NME for the pro-drug of propofol. Advisory committee will occur before May 31, 2007.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Bob Rappaport, Dionne Price, Kate Meaker, John Metcalfe, Dan Mellon, Danae Christodoulou, Srikanth Nallani, Mamata De, Lex Schultheis, Rigoberto Roca, Elsbeth Chikhale, Parinda Jani, Allison Meyer

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Lex Schultheis
CDTL/Secondary Medical:	Rigoberto Roca
Statistical:	Katherine Meaker
Pharmacology:	Mamata De
Statistical Pharmacology:	
Chemistry:	Elsbeth Chikhale
Environmental Assessment (if needed):	
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	John Metcalfe
Microbiology, clinical (for antimicrobial products only):	
DSI:	Sherbet Samuels
OPS:	
Regulatory Project Management:	Allison Meyer
Other Consults:	QT, OSE (RMP, Tradename, Label), DDMAC

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO

If no, explain:

- Advisory Committee Meeting needed? YES, date if known May 2008 NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional): formatting issues with the PLR will be identified, along with a microbiology request, CMC request, pharmacology request and biopharmaceutic requests

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Allison Meyer
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Allison Meyer
12/10/2007 09:34:58 AM
CSO

Parinda Jani
12/11/2007 12:44:33 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (Name, Office/Division, and Phone Number of Requestor): Danae D
Christodoulou PhD through Scott N. Goldie, Ph.D.,
Office of New Drug Quality Assessment, 301 796-2055

DATE
December 7, 2007

IND NO.

NDA NO.
22-244

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
September 27, 2007

NAME OF DRUG
fospropofol sodium

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
February 27, 2008

NAME OF FIRM: MGI Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of new NDA application. Microbiology section 3.2.A.1, Electronic NDA. Additionally, the microbiologist should assess the applicant's proposal for commercial batch validation. Commercial validation was not submitted with the NDA. Injectable dosage form. Please direct questions to Danae Christodoulou at 61342. Submission is in electronic form in EDR.

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Scott Goldie
12/13/2007 02:31:59 PM

Meyer, Allison

From: Kline, Jacqueline [Jacqueline.Kline@mgipharma.com]
Sent: Friday, November 30, 2007 11:09 AM
To: Meyer, Allison
Cc: Ressler, Timothy; O'Sullivan, Stacie
Subject: NDA 22-244 fospropofol disodium

Allison,

Per our conversation this morning, please see our proposed revision to the indication statement below.

1. INDICATIONS AND USAGE

- AQUAVAN[®] (fospropofol disodium) Injection is ~~indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures.~~

b(4)

Please let me know if you have any questions.

Regards,
Jackie

Jacqueline M. Kline, PhD, PMP
Director Regulatory Affairs
MGI PHARMA
410-631-5595

12/4/2007

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/s/

Allison Meyer
12/4/2007 02:18:14 PM
CSO

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: Additional CMC comment
Date: Tuesday, November 20, 2007 11:58:57 AM
Attachments:

Jackie,
Can you respond to this today?
Allison

" Provide the street address of _____
_____, which is proposed as alternate release testing site for
the drug product (M3, Section 3.2.P.3)".

b(4)

DSI CONSULT: Request for Clinical Inspections

Date: November 15, 2007



To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46

From: Allison Meyer, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products,
HFD-170

Subject: **Request for Clinical Site Inspections**
Application: NDA-22-244
Sponsor: MGI Pharma
Drug: Aquavan (fospopofol disodium) Injection

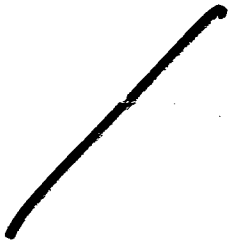
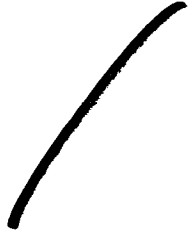
Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Study site 540: Gregory J. Feldman, MD Investigator, Phone 864 253 9626 S. Carolina Pharmaceutical Research 1330 Boiling Springs Road, Suite 2100 Spartanburg, South Carolina 29303 	3000-0524	33	sedation
Study site 321: Allan Seibert, MD Investigator, Phone –not found Pulmonary Associates of Mobile, P.C. 6701 Airport Boulevard Suite B-135 Mobile, AL 36608 	3000-0524	35	sedation

b(4)

b(4)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
<p>Study site 518: Atul Shah, MD Investigator, Phone 410 535 4333 Shah Associates 110 Hospital Drive Suite 303 Prince Frederick, MD 20678</p> 	3000-0522	30	sedation
<p>Study site 544: Gerard A. Silvestri, MD, FCCP Investigator, Phone 843 792 3161 Medical University of South Carolina Division of Pulmonary/Critical Care Medicine 96 Jonathan Lucas Street, CSB-812 Charleston, SC 29425</p> 	3000-0524	27	sedation

b(4)

b(4)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Study site 303: C. Allen Goetsch, MD, CCTI Investigator, Phone 256 536 6600 Clinical Research Associates, LLC 131 Longwood Drive Huntsville, AL 35801	3000-0522	30	sedation

b(4)

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Large differences in frequency of serious AEs reported between sites 540, 544 and 321 in Study 3000-0524. Unexpectedly few serious AEs in study 3000-0522

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) (15 July 2008). We intend to issue an action letter on this application by (division action goal date) (23 July 2008). The PDUFA due date for this application is (25 July 2008).

Should you require any additional information, please contact Allison Meyer at Ph: (301) 796-1258

Concurrence: (as needed)

Rigoberto Roca, MD; Deputy Director
Lex Schultheis, MD, PhD; Medical Officer

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/s/

Allison Meyer
11/15/2007 02:06:55 PM

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: micro request
Date: Wednesday, November 14, 2007 10:52:54 AM
Attachments:

Jackie, please address the following request for Aquavan:

Provide the verification studies demonstrating the suitability of the

~~_____~~, or a reference to the location of
this information in the 26 September 2007 submission.

b(4)

Allison J. Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301)796-1258
10903 New Hampshire Avenue
Building 22, Room # 3135
Silver Spring, MD 20993

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: FW: QT Consult Request - NDA 22244 / Report
Date: Tuesday, October 30, 2007 10:21:58 AM
Attachments:

In addition to the ClinPharm table, please ask the sponsor to provide the PK concentration for pc.xpt. The PC datasets that the sponsor has provided for this study report did not include the PK concentration values.

Please let me know if you have any questions.

Thank you,

Allison

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Controlled Substance Staff (HFD-009) Attn: Corinne Moody		FROM: HFD-170 Division of Anesthesia, Analgesia, and Rheumatology Products Dr. Bob Rappaport		
DATE October 29, 2007	IND NO.	NDA NO. 22-244	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT September 26, 2007
NAME OF DRUG Aquavan	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anesthetic	DESIRED COMPLETION DATE 3/4/08	
NAME OF FIRM: MGI Pharma				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Abuse liability				
COMMENTS/SPECIAL INSTRUCTIONS: Please provide guidance on the abuse liability section of this new NDA 22-244, section 2.7.4.5.6 in the following electronic submission <u>\\CDSESUB1\NONECTD\N22244\N 000\2007-09-26</u> If you have any questions, please contact Allison Meyer, Regulatory Project Manager, at 301-796-1258.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Allison Meyer
10/30/2007 10:36:20 AM

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE

FROM: Division of Anesthesia, Analgesia and Rheumatology, HFD-170, Allison Meyer

DATE
October 25, 2007

IND NO.

NDA NO.21-521

TYPE OF DOCUMENT Risk Management
Plan

DATE OF DOCUMENT 9/26/07

NAME OF DRUG
Aquavan

PRIORITY CONSIDERATION standard

CLASSIFICATION OF DRUG anesthetic

DESIRED COMPLETION DATE 3/4/08

NAME OF FIRM: MGI Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): Risk Management Plan |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV 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

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and comment on the risk management plan included in the September 26, 2007 submission. The mid-cycle meeting will occur on 3/4/08.

\\CDSESUB1\NONECTD\N22244\N 000\2007-09-26
If you have any questions, please contact Allison Meyer, X61258.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Allison Meyer
10/29/2007 07:40:17 AM

REQUEST FOR CONSULTATION

TO (Office/Division): Division of Cardio-Renal Products, Ed Fromm, Devi Kozeli

FROM (Name, Office/Division, and Phone Number of Requestor): Division of Anesthesia, Analgesia and Rheumatology Products, Allison Meyer

DATE October 24, 2007	IND NO.	NDA NO. 22-244	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT September, 26, 2007
--------------------------	---------	-------------------	-----------------------------	---

NAME OF DRUG Aquavan	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG anesthetic	DESIRED COMPLETION DATE 10/16/06
-------------------------	------------------------------------	--------------------------------------	-------------------------------------

NAME OF FIRM: MGI Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input checked="" type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|---|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the following electronic submission and provide comments to the following questions: \\CDSESUB1\NONECTD\N22244\N_000\2007-09-26

1. Does Aquavan cause QT prolongation?
2. Does the thorough QT study report show that Aquavan does not cause QT prolongation?

If you have any questions, please call Allison Meyer at 301-796-1258.

SIGNATURE OF REQUESTOR Allison Meyer	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
---	--

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
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/s/

Allison Meyer
10/29/2007 09:29:03 AM

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: HFD-170, Division of Anesthesia, Analgesia, and
Rheumatolog Products,
Allison Meyer

DATE
10/11/07

IND NO.

NDA NO.
22-244

TYPE OF DOCUMENT
request for tradename
review

DATE OF DOCUMENT
9/26/07

NAME OF DRUG
Aquavan

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
anesthetic

DESIRED COMPLETION DATE
1/11/08

NAME OF FIRM: MGI

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV 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

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review NDA [redacted] for trade name issues concerning the name AQUAVAN. If you have any questions, please call Allison Meyer, 301-796-1258. The submission dated 9/26/07 is an electronic submission. \\CDSESUB1\NONECTD\N22244\N_000\2007-09-26

PDUFA DATE: 7/27/08

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 22-244

HFD-170/Division File

HFD-170/RPM

HFD-170/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

Allison Meyer, x61258

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Allison Meyer
10/18/2007 01:01:02 PM

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

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE/DMETS, White Oak Bldg. 22

FROM: HFD-170, Division of Anesthesia, Analgesia, and
Rheumatology Products

Allison Meyer

DATE
10/11/07

IND NO.

NDA NO.
22-244

TYPE OF DOCUMENT
Labeling

DATE OF DOCUMENT
9/26/07

NAME OF DRUG
Aquavan

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Anesthetic

DESIRED COMPLETION DATE
2/28/08

NAME OF FIRM:MGI

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton and Container labeling |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV 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

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the carton and container labels and package insert for the NDA 22-244 from 9/26/07. This is an electronic submission. \\CDSESUB1\NONECTD\N22244\N 000\2007-09-26

If you have any questions, please contact Allison Meyer at 301-796-1258.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Allison Meyer
10/18/2007 11:19:31 AM



NDA 22-244

NDA ACKNOWLEDGMENT

MGI Pharma
6611 Tributary Street
Baltimore, MD 21224

Attention: Jacqueline Kline, PhD
Director, Regulatory Affairs

Dear Dr. Kline:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: AQUAVAN® (fospropofol disodium) Injection

Date of Application: September 26, 2007

Date of Receipt: September 27, 2007

Our Reference Number: NDA 22-244

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 November 26, 2007, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above shown above be cited 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 Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer
10/15/2007 07:11:48 AM

From: Meyer, Allison
To: "Kline, Jacqueline";
CC:
Subject: carton/container labels
Date: Thursday, October 11, 2007 7:21:27 AM
Attachments:

Jackie,
Can you send me an electronic copy of the carton/container labels in color? Or is the shaded grey box supposed to be grey?

Allison J. Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301)796-1258
10903 New Hampshire Avenue
Building 22, Room # 3135
Silver Spring, MD 20993