CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-217

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 04/30/10
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-217

NAME OF APPLICANT / NDA HOLDER
Neuromed Pharmaceuticals Ltd.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
EXALGO

ACTIVE INGREDIENT(S)
Hydromorphone HCl

STRENGTH(S)
8, 12, 16 and 32 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,702,725

b. Issue Date of Patent
December 30, 1997

c. Expiration Date of Patent
July 7, 2014

d. Name of Patent Owner
c/o Chief Patent Counsel, Johnson & Johnsonn

Address *(of Patent Owner)*
One Johnson & Johnson Plaza

City/State
New Brunswick, New Jersey

ZIP Code
08933

FAX Number *(if available)*

Telephone Number
510-248-2356

E-Mail Address *(if available)*
skais1@its.jnj.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ General Counsel, Neuromed Pharmaceuticals Inc.

Address *(of agent or representative named in 1.e.)*
Six Tower Bridge, Suite 440, 181 Washington Street

City/State
Conshohocken, Pennsylvania

ZIP Code
19428

FAX Number *(if available)*
484-533-6921

Telephone Number
484-533-6900

E-Mail Address *(if available)*

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Graphics: (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2	Patent Claim Number(s) *(as listed in the patent)* 8-10	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Management of persistent, moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock analgesia for an extended period of time.	

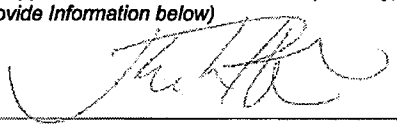
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	5/4/2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name John D. Proffett	
Address Six Tower Bridge, Suite 440 181 Washington Street	City/State Conshohocken, Pennsylvania
ZIP Code 19428	Telephone Number 484-533-6910
FAX Number *(if available)* 484-533-6921	E-Mail Address *(if available)* jproffett@neuromed.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

SECTION 13. PATENT DECLARATON

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Dilaudid SR® (OROS® Hydromorphone HCl) tablets. This product is the subject of this application for which approval is being sought under Section 505 of the Federal Food, Drug and Cosmetic Act.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
5,914,131	Formulation	07/07/2014	ALZA Corporation
5,702,725	Formulation and Method of Use	07/07/2014	ALZA Corporation
5,082,668	Formulation	09/16/2003	ALZA Corporation
4,783,337	Formulation and Method of Use	09/16/2003	ALZA Corporation
4,612,008	Formulation	09/16/2003	ALZA Corporation
4,519,801	Formulation	07/12/2002	ALZA Corporation

Dated: 7/8/99

By: _____

Peter D. Staple
Senior Vice President and General Counsel
ALZA Corporation

EXCLUSIVITY SUMMARY

NDA # 21-217 SUPPL # HFD #

Trade Name EXALGO 8-, 12- and 16-mg Extended-Release Tablets

Generic Name Hydromorphone HCl 8-, 12- and 16-mg Extended-Release Tablets

Applicant Name Alza Corporation

Approval Date, If Known March 1, 2010

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?

3 (three) years

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# 19034 Dilaudid

NDA# 19891 Dilaudid

NDA# 19892 Dilaudid

For additional approved products, see attached list of NDAs and ANDAs.

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:

Study NMT 1077-301

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study NMT 1077-301

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 78223 YES ☐ ! NO ☒
! Explain:
The holder of the IND was Neuromed when the study started. Ownership was transferred to Alza.

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Diana Walker
Title: Regulatory Project Manager
Date: March 1, 2010

Name of Office/Division Director signing form: Bob A. Rappaport
Title: Director, Division of Anasthesia, Analgesia, and Rheumatology Products

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	ALZA CORP	Exalgo (hydromorphone HCl) 8/12/16

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

/s/

DIANA L WALKER
03/01/2010

BOB A RAPPAPORT
03/01/2010

1.3.5.3 EXCLUSIVITY REQUEST

Neuromed Pharmaceuticals Ltd. hereby claims 3 (three) years exclusivity, under 21 CFR 314.108(b)(4)(iv), from the date of approval of this NDA for OROS hydromorphone HCl. OROS hydromorphone is a drug product that contains an active moiety that has been previously approved in another application, but contains reports of new clinical investigations conducted or sponsored by Neuromed Pharmaceuticals Ltd. and essential to approval of the application.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021217	**Trade Name:**	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
Supplement Number:	000	**Generic Name:**	HYDROMORPHONE HCL
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	FOR THE MANAGEMENT OF MODERATE TO SEVERE PAIN WHEN USE OF AN OPIOID ANALGESIC IS APPROPRIATE FOR MORE THAN A FEW DAYS
Action Date:	12/29/99		

Indication # 1 analgesia for moderate to severe pain
Label Adequacy: Inadequate for ALL pediatric age groups
Forumulation Needed: Other
Comments (if any): Sponsor submitted PPSR to (b) (4) on August 14, 2000, which is currently under review (10-27-00)

Lower Range	Upper Range	Status	Date
0 years	16 years	Deferred	1/12/04

This page was last edited on 10/27/00

Signature - Date 10-27-00

DILAUDID CR™ PEDIATRIC USE INFORMATION

Pursuant to 21 CFR 314.55(b), Knoll Pharmaceutical Company requests that FDA defer submission of information from pediatric use studies with Dilaudid CR until after NDA approval. The safety and efficacy of Dilaudid CR in pediatric patients below 18 years of age has not yet been studied.

The sponsor has deferred studying pediatric use of Dilaudid CR until trials in the adult patient population were completed. It was considered reasonable to assess the pharmacokinetic, dosing, efficacy and safety data in the adult population before conducting investigations with the drug in pediatric patients with chronic pain conditions. Clinical trials in the adult patient population have been completed and analyzed, and are submitted with this application.

A clinical study in pediatric patients is planned and will be initiated during the first quarter of 2000. Submission of results from the pediatric trial to the Food and Drug Administration will occur after the NDA approval of the drug product for use in adults.

Dilaudid CR Protocol DO-110, entitled *A Pharmacokinetic Characterization* (b) (4) *and Safety of Dilaudid CR™ (Hydromorphone HCl) in Pediatric Patients with Chronic Pain*, will be performed and has the following objectives:

- (b) (4)

- To characterize means by which pediatric patients on strong opioids can be safely converted and titrated to an effective maintenance dose of Dilaudid CR, and

- To evaluate the safety profile of Dilaudid CR in pediatric patients.

A copy of this protocol will be submitted to the Agency for comment prior to study initiation.

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

ALZA Corporation 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.

02/12/2010

Francesco Pannone

Date

President, ALZA Corporation

Knoll Pharmaceutical Company

BASF Pharma

DEBARMENT STATEMENT

Knoll Pharmaceutical Company hereby certifies, in accordance with the Federal Food, Drug and Cosmetic Act [FDC Act § 306(k)], that it has not utilized the services of any firm or person(s) debarred in the preparation of information for this NDA as described in Section 306(e) of the Federal Food, Drug and Cosmetic Act, as Amended.

Melvin Spigelman 12/13/99

Melvin Spigelman, M.D. Date
Vice President, Research and Development

DEBARMENT STATEMENT

ALZA Corporation hereby certifies, in accordance with the Federal Food, Drug, and Cosmetic Act [FDC Act § 306(k)], that it has not utilized the services of any firm or person(s) debarred in the preparation of information for this NDA as described in Section 306(e) of the Federal Food, Drug, and Cosmetic Act, as Amended.

19 March 1999

Janne Wissel — Date

Senior Vice President, Operations

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21-217 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: EXALGO Extended-release Tablets Established/Proper Name: Hydromorphone HCl Dosage Form: 8-, 12-, and 16-mg Extended-release Tablets		Applicant: Alza Corporation Agent for Applicant (if applicable): Premier Research
RPM: Diana Walker		Division: DAARP

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	March 1, 2010
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Approvable, October 27, 2000
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	Ocotber 14, 2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) March 1, 2010 October 27, 2000
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	February 25, 2010
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	May 22, 2009 December 29, 1999
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	February 17, 2010
• Original applicant-proposed labeling	May 22, 2009
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	November 17, 2009 Original applicant-proposed: May 22, 2009 December 29, 1999
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	Reviews: October 21, 2009 June 1, 2009 August 28, 2000 Acceptable letter: June 2, 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP October 14, 2009 ☒ DRISK November 5, 2009 ☒ DDMAC October 31, 2009 ☐ CSS ☒ Other reviews SEALD: November 3, 2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Cycle 1 Filing Review: February 28, 2000
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	February 12, 2010

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable October 14, 2009
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg August 8, 2008 and August 4, 1999
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	11/1/2005, 8/11/2005, 1/24/2003, 12/7/2000, 7/11/2000, 12/9/1999, 10/3/1997
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	September 23, 2009
• 48-hour alert or minutes, if available *(do not include transcript)*	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None March 1, 2010 and October 24, 2000
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None February 23, 2010 and October 11, 2000
PMR/PMC Development Templates *(indicate total number)*	☐ None October 30, 2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	CDTL Review - February 23, 2010
• Clinical review(s) *(indicate date for each review)*	October 29, 2010 and October 2, 2000
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See clinical reviews
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See clinical reviews
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None September 4, 2009, August 21, 2009, June 2, 2000
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not needed March 1, 2010, November 13, 2009, October 23, 2009, September 21, 2009, August 27, 2009, February 9, 2000
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	February 25, 2010 March 1, 2010 ☐ None March 1, 2010 February 24, 2010 November 13, 2009 October 27, 2009

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Summary Review: October 22, 2009 Letters: 12/28/2009, 11/30/2009, 10/27/2009
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None October 29, 2009 June 15, 2000, February 29, 2000
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None October 21, 2009, September 20, 2000 and February 9, 2000
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None February 5, 2010
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None February 5, 2010 July 24, 2000 and January 6, 2000
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None October 23, 2009
• Product quality review(s) *(indicate date for each review)*	☐ None November 10, 2009, October 23, 2009, October 27,

	2000 and February 8, 2000
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharmaceutics Review: September 30, 2009
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	see CMC Review: October 27, 2000
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: November 2, 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	ALZA CORP	Exalgo (hydromorphone HCl) 8/12/16

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

/s/

DIANA L WALKER
03/04/2010

Walker, Diana

From: Walker, Diana
Sent: Monday, February 22, 2010 3:37 PM
To: 'Susan Franks'
Subject: NDA 21217 Clinical Information Request-Pediatrics 22Feb10
Importance: High

Dear Susan,

I have received the following request from the Clinical review team. As requested, please submit the following to your NDA by February 24, 2010.

Regarding the post-marketing commitments to fulfill the PREA requirements for NDA 21-217, the Division has determined that the efficacy of Exalgo can be extrapolated from adults to the pediatric population. Therefore, only pharmacokinetic and safety study(ies) are required. You have proposed two pharmacokinetic studies, one in 2 to 7 year olds, and one in 7 to 17 year olds. Safety data can be collected during these trials if you choose. Please submit an amended Pediatric Plan to reflect the above request by Wednesday February 24, 2010. Include the following dates for each proposed study: protocol submission, study start, study completion, and final report submission.

Please contact me for any clarifications.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	ALZA CORP	Exalgo (hydromorphone HCl) 8/12/16

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

/s/

DIANA L WALKER
03/01/2010

Walker, Diana

From: Walker, Diana
Sent: Thursday, November 05, 2009 9:50 AM
To: 'Susan Franks'
Subject: NDA 21217 DLDE table in SPL file 05Nov09

Dear Susan,

I have received the following comments from the CMC reviewers regarding your SPL submission.

Comments regarding the Drug Listing Data Element (DLDE) table in the SPL file:

The Drug Listing Data Element (DLDE) Tables in the SPL file needs to be updated with the following:

1. The names of the inactive ingredients should match those listed under "Description" in the proposed Prescribing Information;
2. The imprint codes should be provided.
3. A table for the 32 mg strength should be included.
4. The color for the 12 mg strength should be corrected.

Please let me know if you have any questions concerning these comments.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

From: Walker, Diana
Sent: Tuesday, October 27, 2009 3:29 PM
To: 'Susan Franks'
Cc: James Ottinger
Subject: NDA 21217 Exalgo REMS comments 27Oct09
Importance: High
Attachments: NDA 21217 REMS Comments 27Oct09.doc

Dear Susan,

The following comments are Office of Surveillance and Epidemiology's (OSE's) review of the proposed REMS for Exalgo (hydromorphone HCl). Please submit a revised REMS to your NDA as soon as possible, in order for the review to be completed in a timely manner. I am attaching this email content as a Word document for your convenience as well.

A. General comments

1. The educational materials for prescribers must address at least the following:

    a. Proper patient selection

    b. Appropriate product dosing and administration

    c. General opioid use, including information about opioid abuse and how to identify those at risk for addiction

    d. The risk of abuse, misuse, overdose, and addiction from exposure to opioids, including Exalgo

    e. The risks of Exalgo including:

        i. The risk of overdose caused by exposure to an essentially immediate-release form of hydromorphone due to breaking, chewing, crushing or dissolving Exalgo

        ii. The risk of overdose due to prescribing Exalgo to opioid non-tolerant patients

    f. Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances

    g. The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read it

2. REMS do not address ((b) (4)). Remove all references to (b) (4) The word "misuse" can be used instead of the word (b) (4).

3. Patient education can not be included in the communication plan heading of the REMS.

4. There are no elements to assure safe use. Remove all references to the Exalgo Alliance Program.

5. Additional education material for prescribers:

   a. FDA does not regulate best practice and universal precautions, so they can not be included in the REMS.

   b. Remove [redacted] (b) (4)

6. REMS materials are not appropriate for use in a promotional manner.

7. The proposed REMS letters will be disseminated at launch. Provide an endpoint (time frame) for disseminating the letters.

8. Goals should read:

   Goal 1: To inform patients and providers about the potential for abuse, misuse, overdose, and addiction of Exalgo.

   Goal 2: To inform patients and providers about the safe use of Exalgo in opioid-tolerant patients.

B. Comments about the Medication Guide

The review of the Medication Guide is not complete. Comments regarding the Medication Guide will be sent in separate communications.

C. Communication Plan

Will consist of:

1. Introductory letters for:
   a. Prescriber
   b. Pharmacy
   c. Professional associations (medical and pharmacy)

2. Remove the letters to the [redacted] (b) (4) from the REMS.

D. Specific Comments for Prescriber, Pharmacist, Association, Pain Care Center of Excellence and Compendia Letters

1. There is concern that the proposed REMS materials minimize the risks of Exalgo by omitting the REMS specific risk information within the body of the letters and the brochure. For example, risk information from the WARNINGS AND PRECAUTIONS section of the proposed product labeling (PI) such as misuse, abuse, and diversion of opioids which is part of the goals of the REMS program are omitted from the introductory letters and brochure.

2. The proposed REMS materials present the claim, [redacted] (b) (4) The proposed claim minimizes the risks associated with Exalgo therapy. Eliminate this language.

3. There is concern that the content and order of presentation of the risk information within the proposed REMS materials minimizes the risks associated with EXALGO. For example, the Prescriber Introductory letter presents the most commonly reported adverse events on page one while the boxed warning is presented on page three, after the signature line. This minimizes the risks being communicated.

4. Page one of the proposed introductory letters present the claim:

[redacted] (b) (4)

This claim is an inadequate communication of the indication; revise to include the full approved indication. For example, we note that the full indication includes a limitation to its use relating to acute/postoperative pain, mild pain, or pain that is not expected to persist for an extended period of time. We note that although some of the limitations are presented on page three of the letter within the boxed warning, this does not adequately communicate the indication. Revise the information to adequately communicate the indication.

5. Remove the promotional language shown in bold from the first paragraph of the letters. [redacted] (b) (4)

6. Do not bold the text in the letters. Bolded text used in the body of the letter minimizes the importance of other information in the letter.

7. Remove the second paragraph of the letters. These claims and presentation are promotional in tone and focus on promoting the benefits of the treatment rather than on educating about the serious risks of treatment [redacted] (b) (4)

8. Remove the text box from the top of the letters. This presentation of the information within the box, as a header, minimizes the REMS risks associated with Exalgo. The language, within the box, as a header at the beginning of the letters, [redacted] (b) (4)

9. Remove the last sentence of the fifth paragraph in each letter that states [redacted] (b) (4) It is promotional in tone.

E. Prescriber Brochure

1. The proposed brochure is currently used to describe the EXALGO Alliance Program. Revise the brochure and provide non-promotional safety information; remove all references to the Alliance Program.

2. Provide a plan for the dissemination of the brochure in the REMS and Supporting Document.

F. Timetable for Submission of Assessments

Neuromed Pharmaceuticals will submit REMS assessment to the FDA at 6 months and 1 year after the approval date of the NDA for Exalgo, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Neuromed Pharmaceuticals will submit each assessment so that it will be received by the FDA on or before the due date.

G. Patient and provider surveys

Submit for review a detailed plan to evaluate patients' and healthcare providers' understanding about the risks associated with and safe use of Exalgo. This information does not need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." The submission should include all methodology and survey instruments that will be used to evaluate the patients' and healthcare providers' understanding about the risks associated with and safe use of Exalgo. This should include, but not be limited to:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients/healthcare providers to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

General Comments:

Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

Revise the REMS to follow the appended REMS template.

Appendix A: REMS Template

'ou are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:
List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

scribe the implementation system to monitor and evaluate implementation for, and work to improve implementation ., Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix b: supporting document

is REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to ..clude one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)

5. REMS Assessment Plan (for products approved under a NDA or BLA)

.. Other Relevant Information

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Friday, October 23, 2009 10:37 AM
To: 'Susan Franks'
Subject: NDA 21-217 (Exalgo) CMC Information Request 23Oct09
Importance: High

Dear Susan,

I have received information from our CMC Review Team, who request that you submit the response/provide a written agreement to your NDA as soon as possible.

The moisture content in the product increases on stability and a specification of NMT (b) (4), has been proposed. However, no annual microbial limits test data on stability have been included in the NDA. Since end-product testing has been performed only at release, provide an agreement to perform microbial limits testing annually on stability for the first three post-approval batches for the lowest and highest strengths bracketing the rest of the dosage strengths. Upon completion of these studies, you may re-evaluate your proposal to omit a microbial limits specification in the drug product upon release and on stability.

Regards,

Diana

na L. Walker, Ph.D.
gulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

From: Walker, Diana
Sent: Friday, October 23, 2009 9:14 AM
To: 'Susan Franks'
Subject: FW: NDA 21-217 (Exalgo) Clinical Information Request 23Oct09

Importance: High

Dear Susan,

I have received a second request for information from our Clinical Reviewer, who requests that you submit the response as soon as possible.

The 4 month Safety Update (SU) was to include SAEs as of January 31, 2009, for Study NMT 1077-302. The SU includes Study 42801-PAI-3001, but not Study NMT 1077-302.

Please explain where in the submission that information can be found or provide the data.

Additionally, please provide a synopsis of Study NMT 1077-302, as it is not included in Section 2.7.6 Synopses of Individual Studies.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Thursday, October 22, 2009 4:48 PM
To: 'Susan Franks'
Subject: NDA 21217 FDA Information Request-Carton and Container 22Oct09
Importance: High

Dear Susan,

I have received feedback on your revised Carton and Container submission from the Division of Medication Errors Prevention and Analysis (DMEPA). They have the following comments:

"The Applicant did a nice job implementing our suggestions with the exception of one; we are concerned about the colors chosen for the 12 mg and 16 mg. These bottles will be next to one another on the shelf. The colors appear to be two shades of (b) (4), which is not advisable. Given the number of colors to choose from and the ramifications of an error with this extended release hydromorphone, we recommend you change either the 12 mg or the 16 mg color to better differentiate these strengths."

Please submit a response to the comment above as soon as possible.

Regards,

Diana

m: Walker, Diana
t: Thursday, October 15, 2009 10:23 AM
o: 'Susan Franks'
Subject: NDA 21217 FDA Information Request-Carton and Container 15Oct09
Importance: High

Dear Susan,

I have received the review of your carton and container labeling from the Division of Medication Errors Prevention and Analysis (DMEPA). Please address the following comments and submit your response and revised labeling as soon as possible to your NDA.

Container Label

1. **As currently proposed, the labels for all the available strengths of Exalgo appear similar when compared side-by-side. The labels should be revised to incorporate the use of color, boxing, or some other means to allow for adequate differentiation between the available product strengths.**

2. **Ensure the size and prominence of the established name is at least ½ the size of the proprietary name to be in accordance with CFR 201.10(g)(2). Additionally, the manufacturer name and logo should be decreased in size so that it does not appear larger and more prominent then the established name on the principle display panel.**

3. **Increase the size and prominence of the dosage form statement "Extended-release Tablet", to be commensurate with the established name as it is considered part of the established name.**

4. **In accordance with 21 CFR 1302.04, the controlled substance symbol should be increased in prominence and font to ensure easy identification of the schedule of Exalgo. Additionally, the controlled substance symbol should be relocated away from the proprietary name as the symbol where it is currently placed could be mistaken for the letter 'o'.**

5. **Encase the statement "For opioid tolerant patients only" using a box or color box to ensure that the statement is prominent.**

6. **The primary display panel of the container label is too cluttered and contains statements that could be deleted** (b) (4) **) or relocated to a side panel** (b) (4)

7. **The side panel of the container label is cluttered and difficult to read. Deletion of redundant or unnecessary statements will provide space for pertinent statements. DMEPA considers the statements regarding children unnecessary as the bottles are not unit of use and will not be dispensed directly to the patient. The following statements should be considered for deletion:**

(b) (4)

8. **Include one of the following statements: "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" on the principle display panel of the container labels and carton labeling. Use the first sentence ("enclosed") if the Medication Guide will be inside the carton/container and the entire carton/container is considered a unit of-use bottle that is dispensed to a single patient. Use the second sentence ("accompanying") if the Medication Guide is glued to the container/carton, as a tear-off sheet, etc). Ensuring that the Medication Guide statement is prominently displayed will help to alert healthcare practitioners to provide this essential patient information along with Exalgo.**

9. **The proposed graphic on the principle display panel should not intersect with the letter 'o' in the proprietary name or interfere with the readability or interpretation of the proprietary name and should be removed or relocated accordingly.**

Please feel free to contact me if you have any questions on this request.

Regards,

Diana

ana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713

12/7/2009

Email: Diana.Walker@fda.hhs.gov

Walker, Diana

From: Walker, Diana
Sent: Thursday, October 22, 2009 10:00 AM
To: 'Susan Franks'
Cc: 'James Ottinger'
Subject: NDA 21-217 (Exalgo) Clinical Information Request 22Oct09

Importance: High

Dear Susan,

I have received a request for information from our Clinical Reviewer, who requests that you submit the response as a priority, as soon as possible.

Study 428001-PAI-308 (Planned 110, adult patients with cancer pain, Taiwan; 17-28 days) is included in the table of "Listing of Clinical Studies Included in this Submission and Ongoing Studies". However, the study synopsis is not provided in the submission and the study was not included in the pooled safety data (although the study drug was OROS 16 mg to 96 mg qd).

The study terminated early.

Please explain where in the submission information regarding the study can be found (other than the Listing of Clinical Studies table) and why the study was not included as part of the pooled safety data.

If the study information is not in the submission, please provide a synopsis of the study including reason for termination of study.

Please respond to this request in priority fashion.

Regards,

Diana

Walker, Diana

rom: Walker, Diana
Sent: Wednesday, October 21, 2009 1:39 PM
To: 'Susan Franks'
Cc: 'James Ottinger'
Subject: NDA 21-217 Exalgo Clinical Information Request 21Oct09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible, so that the review team is able to complete their review in a timely manner. Please submit responses to the following 4 questions:

The Division of Scientific Investigations (DSI) has identified that "the central laboratory was not able to perform urine testing for tramadol and fentanyl" during some period of Study NMT 1077-301. As per the protocol below, urine testing for exclusion criteria, permitted drugs during the study, and Schedule of events is noted below:

> **Exclusion criteria #8 - Patients with a positive alcohol or drugs of abuse test at the Screening Visit or Conversion and Titration Visit 1. Patients with positive urine test for medications that were not prescribed to the patients or were not medically explainable after Conversion and Titration Visit 1 were to be discontinued from the study.**
>
> **All other analgesics (including tramadol and opioids) were not permitted during study.**
>
> **Schedule of Visits and Procedures notes that Urine Drug and Alcohol Tests were to be performed at Screening, C/T Phase visit 1 and at final visit. Urine samples were collected randomly at two visits during the double-blind phase for drug and alcohol tests.**

Please respond to the following:

1) Clarify which sites were unable to perform urine testing for tramadol and fentanyl and why the testing could not be performed.

2) Clarify the inclusive dates when such testing was not able to be performed.

3) Clarify how many patients were affected (by site).

4) Clarify how many subjects had testing requested for tramadol and fentanyl once the new testing method was initiated, and how many subjects did not have testing requested.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
': 301-796-4029
.: 301-796-9723/9713
_.nail: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Monday, October 19, 2009 2:59 PM
To: 'Susan Franks'
Subject: NDA 21217 FDA Request for Information/PMC Proposal/19Oct09
Importance: High

Dear Susan,

I am sending you a request for post-marketing committment proposals for NDA 21217 from the Division. Note that this email is not meant to imply that this is an inclusive list of any or all potential PMRs/PMCs, but is a consideration of two specific proposals, nor is it an implication of any specific potential action to be taken for your NDA. Note also that the two carcinogenicity studies in question are already currently ongoing, so this is not a request for new study proposals, but for proposed dates. The Division is requesting that you submit proposed dates for final report submission for the following two items:

1. Description of Commitment:

   Carcinogenicity study in mouse (currently ongoing per August 8, 2008, agreement)

   Protocol Submitted: October 6, 2005
   Study Start: March 24, 2009
   Final Report Submission: by MM/YY

2. Description of Commitment:

   Carcinogenicity study in rat (currently ongoing per August 8, 2008, agreement)

   Protocol Submitted November 21, 2008
   Study Start: March 18, 2009
   Final Report Submission: by MM/YY

If possible, please submit a response to me by Wednesday, October 21, 2009. Please do not hesitate to contact me with any questions regarding this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
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Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	Exalgo (hydromorphone HCl) 8/12/16/32

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

/s/

DIANA L WALKER
12/07/2009

Walker, Diana

rom: Walker, Diana
Sent: Monday, October 19, 2009 10:20 AM
To: 'Susan Franks'
Subject: RE: NDA 21-217/FDA Multidiscipline Information Request/29Sep09
Importance: High

Dear Susan,

Here is the response I received from the reviewer concerning your question below:

Based on the information provided in your October 5, 2009 response to the Agency request for information on September 29 and October 1, 2009, we agree that no further safety qualification for hydromorphone N-oxide will be needed to support the specification of NMT (b) (4)%. We concur with your conclusion that the results from the genetic toxicology studies and the 4-week toxicity study in rats have provided sufficient data to adequately qualify hydromorphine N-oxide.

Please let me know if you have further questions.

Regards,

Diana

From: Susan Franks [mailto:Susan.Franks@premier-research.com]
nt: Monday, October 12, 2009 10:06 AM
Walker, Diana
ubject: FW: NDA 21-217/FDA Multidiscipline Information Request/29Sep09

Hi Diana,

At the risk of being an annoyance, did the CMC reviewer have any comments, feedback or agreement on our proposal for the N-oxide impurity specification? See details below. I certainly understand if they are not done with the review yet, but just wanted to check in.

Many thanks,
Susan

Susan M. Franks, M.S.
Director, Regulatory Affairs
Premier Research Group
755 Business Center Drive
Suite 200
Horsham, PA 19044
ph: 215-907-1330 ext 1025

From: Susan Franks
Sent: Monday, October 05, 2009 4:04 PM
To: 'Walker, Diana'
bject: RE: NDA 21-217/FDA Multidiscipline Information Request/29Sep09

Hi Diana,

I wanted to let you know that the response the CMC request for information below was just sent through the gateway (as you

suggested, I also included the missing C of A for the one impurity).

Essentially, Neuromed has agreed to all of the requests proposed by the Division, with the exception of one. With respect to the romorphone N-oxide impurity (question 2 below), Neuromed had originally submitted a specification of NMT (b)(4)%, and the reviewer asked for justification of the adequacy of the 4 week tox study to support a specification of NMT (b)(4)%, rather than (b)(4)% for an unqualified impurity. In response, we have provided this justification, and as well, have proposed to reduce the specification for this impurity to NMT (b)(4)%.

Can you tell me what the process will be if the Reviewer does not agree with our proposal? We would certainly be open to a teleconference if needed, and want to be sure we have provided the appropriate information to allow the Reviewer to make their assessment.

As always, thanks for any insight you can provide.

Kind Regards,

Susan

Susan M. Franks, M.S.
Director, Regulatory Affairs
Premier Research Group
755 Business Center Drive
Suite 200
Horsham, PA 19044
ph: 215-907-1330 ext 1025

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Tuesday, September 29, 2009 1:26 PM
To: Susan Franks
Subject: NDA 21-217/FDA Multidiscipline Information Request/29Sep09
Importance: High

Dear Susan,

I have received a request for information from our CMC and Nonclinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

1. The proposed drug product specification for (b)(4) of NMT (b)(4)% exceeds the impurity qualification threshold level of 0.2%. The specifications of this impurity must be reduced to NMT 0.2% or adequate safety qualification must be provided. Adequate safety qualification must include:

a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g. point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. Repeat dose toxicology of appropriate duration to support the proposed indication (90 days for a chronic indication.)

To date, you have only provided a 4-week toxicity study for (b)(4), which will preclude the ability of the review team to determine that the proposed specification is acceptable.

The proposed drug product specification for hydromorphone N-oxide of NMT (b)(4)% exceeds the impurity qualification threshold level of 0.2%. Therefore the specification of these impurity in the drug product must be reduced to NMT 0.2% or adequate safety qualification must be provided. Adequate safety qualification must include:

a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g. point mutation assay

and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. Repeat dose toxicology of appropriate duration to support the proposed indication (90 days for a chronic indication.)

To date, you have provided a 4-week toxicity study for hydromorphone-N-oxide, and the requested minimal genetic toxicology screen, which are under review. However, you have not provided justification for the adequacy of a 4-week toxicology study for this impurity. Provide justification that the 4-week toxicity study is an adequate qualification of safety for this chronic indication.

3. Revise the total degradation products specification accordingly.

4. The following dissolution specifications are recommended for all tablet strengths at batch release and on stability.

Time Interval (hours)	Cumulative Amount Released (% of Label Claim)
0 - 4hr	(b) (4),
0 - 6hr	(b) (4)
0 - 10hr	(b) (4)
0 - 20hr	(b) (4)

5. Provide justification for using the Relative Response Factor (RRF) 1.0 in the assay of the degradation product (b) (4), with the Method AAM 1.771.

Please let me know if you would like me to provide any clarifications for the above questions.

gards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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

/s/

DIANA L WALKER
10/20/2009

Walker, Diana

rom: Walker, Diana
Sent: Friday, October 16, 2009 9:27 AM
To: 'Susan Franks'
Subject: FW: NDA 21217 FDA Clarification-Carton and Container 16Oct09
Importance: High

Dear Susan,

I am enclosing clarifications for two of the Carton and Container comments below. Please address these together with the previous comments, which I am forwarding below for convenient reference.

Clarification for Comment # 2:

Increase the prominence of the font (e.g. size, boldness) for the established name as compared to the trade name.

Clarification for Comment # 3:

Use the same font for both the established name (hydromorphone HCl) and the dosage form (extended release tablets) and keep them in the same line.

Please let me know if you have further questions or if there is any confusion concerning these clarifications.

regards,

Diana

From: Walker, Diana
Sent: Thursday, October 15, 2009 10:23 AM
To: 'Susan Franks'
Subject: NDA 21217 FDA Information Request-Carton and Container 15Oct09
Importance: High

Dear Susan,

I have received the review of your carton and container labeling from the Division of Medication Errors Prevention and Analysis (DMEPA). Please address the following comments and submit your response and revised labeling as soon as possible to your NDA.

Container Label

1. **As currently proposed, the labels for all the available strengths of Exalgo appear similar when compared side-by-side. The labels should be revised to incorporate the use of color, boxing, or some other means to allow for adequate differentiation between the available product strengths.**

2. **Ensure the size and prominence of the established name is at least ½ the size of the proprietary name to be in accordance with CFR 201.10(g)(2). Additionally, the manufacturer name and logo should be decreased in size so that it does not appear larger and more prominent then the established name on the principle display panel.**

3. **Increase the size and prominence of the dosage form statement "Extended-release Tablet", to be commensurate with the established name as it is considered part of the established name.**

4. **In accordance with 21 CFR 1302.04, the controlled substance symbol should be increased in prominence and font to ensure easy identification of the schedule of Exalgo. Additionally, the controlled substance symbol should be relocated away from the proprietary name as the symbol where it is currently placed could be mistaken for the letter 'o'.**

5. **Encase the statement "For opioid tolerant patients only" using a box or color box to ensure that the statement is prominent.**

6. **The primary display panel of the container label is too cluttered and contains statements that could be deleted** (b) (4) **) or relocated to a side panel** (b) (4)

7. **The side panel of the container label is cluttered and difficult to read. Deletion of redundant or unnecessary statements will provide space for pertinent statements. DMEPA considers the statements regarding children unnecessary as the bottles are not unit of use and will not be dispensed directly to the patient. The following statements should be considered for deletion:**

(b) (4)

8. **Include one of the following statements: "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" on the principle display panel of the container labels and carton labeling. Use the first sentence ("enclosed") if the Medication Guide will be inside the carton/container and the entire carton/container is considered a unit of-use bottle that is dispensed to a single patient. Use the second sentence ("accompanying") if the Medication Guide is glued to the container/carton, as a tear-off sheet, etc). Ensuring that the Medication Guide statement is prominently displayed will help to alert healthcare practitioners to provide this essential patient information along with Exalgo.**

9. **The proposed graphic on the principle display panel should not intersect with the letter 'o' in the proprietary name or interfere with the readability or interpretation of the proprietary name and should be removed or relocated accordingly.**

Please feel free to contact me if you have any questions on this request.

Regards,

:na

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029

10/20/2009

Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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

/s/

DIANA L WALKER
10/20/2009

Walker, Diana

rom: Walker, Diana
Sent: Thursday, October 15, 2009 4:42 PM
To: 'Susan Franks'
Subject: NDA 21217 FDA Information Request-Clinical Clarification 15Oct09
Importance: High

Dear Susan,

I have received an information request from the Clinical review team. Please submit clarification for the following as soon as possible:

1. There appears to be a discrepancy in some of the Tables when cross-referenced with the narratives.

a. Figure 3 (p. 74 of Study NMT-1077-301 shows that 3 patients in the Conversion/Titration Phase; 3 patients in OROS treated DB and 7 patients in Placebo DB withdrew due to Opioid Withdrawal Symptoms. However, Table 32 (Number and Percentage of Patients Who Withdrew Because of an Adverse Event by System Organ Class and MedDRA Preferred Term in the Conversion and Titration Phase) on page 136 of the report lists only 1 patient who withdrew in the Conversion/Titration Phase. Please clarify.

b. Table 33 (p. 138) does not list any patients who withdrew due to Opioid Withdrawal Symptoms in the DB Phase. Please clarify.

2. Narratives for the 3 patients in the C/T Phase and 3 OROS patients are provided in Table 3 (p. 125). However, Table 3 appears to list only 6 patients (not 7) for narratives. Please clarify.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
10/20/2009

Walker, Diana

rom: Walker, Diana
Sent: Tuesday, September 29, 2009 1:26 PM
To: 'Susan Franks'
Subject: NDA 21-217/FDA Multidiscipline Information Request/29Sep09
Importance: High

Dear Susan,

I have received a request for information from our CMC and Nonclinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

1. The proposed drug product specification for [redacted] (b) (4) of NMT [redacted] (b) (4) % exceeds the impurity qualification threshold level of 0.2%. The specifications of this impurity must be reduced to NMT 0.2% or adequate safety qualification must be provided. Adequate safety qualification must include:

a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g. point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. Repeat dose toxicology of appropriate duration to support the proposed indication (90 days for a chronic indication.)

To date, you have only provided a 4-week toxicity study for [redacted] (b) (4), which will preclude the ability of the review team to determine that the proposed specification is acceptable.

The proposed drug product specification for hydromorphone N-oxide of NMT [redacted] (b) (4) % exceeds the impurity qualification threshold level of 0.2%. Therefore the specification of these impurity in the drug product must be reduced to NMT 0.2% or adequate safety qualification must be provided. Adequate safety qualification must include:

a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g. point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. Repeat dose toxicology of appropriate duration to support the proposed indication (90 days for a chronic indication.)

To date, you have provided a 4-week toxicity study for hydromorphone-N-oxide, and the requested minimal genetic toxicology screen, which are under review. However, you have not provided justification for the adequacy of a 4-week toxicology study for this impurity. Provide justification that the 4-week toxicity study is an adequate qualification of safety for this chronic indication.

3. Revise the total degradation products specification accordingly.

4. The following dissolution specifications are recommended for all tablet strengths at batch release and on stability.

Time Interval (hours)	Cumulative Amount Released (% of Label Claim)
0 – 4hr	[redacted] (b) (4)
0 – 6hr	
0 – 10hr	
0 – 20hr	

5. Provide justification for using the Relative Response Factor (RRF) 1.0 in the assay of the degradation product [redacted] (b) (4) with the Method AAM 1.771.

Please let me know if you would like me to provide any clarifications for the above questions.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Monday, September 28, 2009 2:00 PM
To: 'Susan Franks'
Subject: NDA 21-217/FDA CMC Information Request/28Sep09
Importance: High

Dear Susan,

I have received a request for information from our CMC review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

1. Clarify whether the blister packaging proposed in the original NDA will be a commercial packaging configuration besides the bottle packaging.

2. If the answer is "yes" to the above question, provide responses to the deficiencies 4.i. and 4.j. concerning the blister packaging in the Agency's October 27, 2000, Approvable letter.

Please let me know if you would like me to provide a copy of the letter referenced in Question #2.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
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Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Tuesday, September 22, 2009 12:41 PM
To: Susan Franks; 'James Ottinger'
Subject: NDA 21-217 Exalgo/Pediatric Information Request/22Sep09
Importance: High

Dear Susan,

I know you are preparing for the AC meeting, and so will not be able to respond immediately; however I wanted to send this request to you as soon as possible. If possible, please submit a response no later than Monday, September 28, 2009, as we are preparing documents to present your pediatric plan to the Pediatric Review Committee. Please submit via email followed by an official submission. In reference to your Pediatric Proposal:

Confirm that you will be collecting safety data on all patients enrolled in the proposed studies.

Please contact me if you have questions regarding this request.

Regards,

Diana

Diana L. Walker, Ph.D.
`gulatory Project Manager
\/CDER/ODE II/DAARP
ɔı: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Thursday, September 10, 2009 9:39 AM
To: 'Susan Franks'
Cc: 'James Ottinger'
Subject: NDA 21-217 Exalgo/Statistical Information Request/10Sept09
Importance: High

Dear Susan and Jim,

I have received a follow-up request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

1. **Clarify how many records in WEIRDDTS are duplicates.**

2. **Classify the remaining records (as out of window, etc.) and give the counts in each category.**

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

.na L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICALS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
10/20/2009

Walker, Diana

rom: Walker, Diana
Sent: Wednesday, September 09, 2009 10:08 AM
To: 'Susan Franks'
Cc: 'James Ottinger'
Subject: NDA 21-217 Exalgo/Clinical Information Request/09Sep09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible, but no later than September 25, 2009, so that the review team is able to complete their review in a timely manner. Please submit the following items:

Please submit the narratives of subjects who had drug accountability discrepancies, but were excluded under the "5+5" algorithm.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

na L. Walker, Ph.D.
gulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Tuesday, September 01, 2009 11:29 AM
To: 'James Ottinger'; Susan Franks
Subject: NDA 21-217 Exalgo/Statistical Information Request/01Sept09
Importance: High

Dear Susan and Jim,

I have received a request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

Regarding the pivotal trial, study 301, you submitted a SAS program titled XEF.SAS, which creates the efficacy analysis dataset. In the course of the computations, this program creates a temporary data file named WEIRDDTS. Clarify why a record is put in WEIRDDTS, and what effect these records have on the efficacy analysis.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

na L. Walker, Ph.D.
gulatory Project Manager
DA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Thursday, August 27, 2009 4:03 PM
To: 'James Ottinger'; Susan Franks
Subject: NDA 21-217 Exalgo/Clinical Information Request/27Aug09

Dear Susan and Jim,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

Please provide the Narrative for patient # 2695005 in Study DO-109. The CRF has been provided but not the narrative.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
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: 301-796-9723/9713
ail: Diana.Walker@fda.hhs.gov

Diana L. Walker, Ph.D.
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Email: Diana.Walker@fda.hhs.gov

Walker, Diana

rom: Walker, Diana
Sent: Friday, August 21, 2009 3:40 PM
To: Susan Franks; 'James Ottinger'
Subject: NDA 21-217 Exalgo/Clinical Information Request/21Aug09
Importance: High

Dear Susan and Jim,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

Provide CRFs for dropouts from the Conversion and Titration Phase and Randomized Phases in the following categories for Study NMT 1077-301:

- **Withdrew consent**
- **Protocol violation**

Please contact me if you have any questions or need clarification on this request.

Regards,

.na

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Walker, Diana

From: Walker, Diana
Sent: Monday, August 10, 2009 3:49 PM
To: Susan Franks
Subject: NDA 21-217 Exalgo/Clinical - Pediatric Information Request/10Aug09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217 concerning your Pediatric Plan. Please submit the following to your NDA as soon as possible, but **no later than September 11, 2009**, so that the review team is able to complete their review in a timely manner.

We acknowledge the submission of the pediatric plan for Exalgo, and have the following comments:

1. **We are in agreement that a deferral of pediatric studies is appropriate.**
2. **We are not in agreement that pediatric studies should be waived for pediatric patients less than six years of age. Duragesic (transdermal fentanyl) is approved down to age two years for use in opioid tolerant patients.**
3. **PK, efficacy and safety studies must be conducted in patients aged 2-17 years of age.**
4. **Efficacy studies must be double-blind, controlled, superiority trials.**
5. **Development of an age appropriate formulation that retains the extended-release properties of Exalgo must be attempted, and/or justification must be provided for the lack of age appropriate formulation.**

   Protocols do not need to be submitted with the pediatric plan; only a commitment to perform the studies.

6. **A timeline for the proposed pediatric studies must be included in the pediatric plan, and should include the following dates: Final protocol submission to the Agency, Study Start, Study completion, and Final study report submission to the Agency.**

The pediatric plan will be submitted to the Agency's Pediatric Research Committee for approval.
If you have questions, we can respond in writing or schedule a teleconference to discuss.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

From: Walker, Diana
Sent: Friday, August 07, 2009 8:54 AM
To: Susan Franks
Subject: NDA 21-217 Exalgo/Statistical Information Request/07Augl09
Importance: High

Dear Susan,

I have received a request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items regarding **NMT 1077-301**:

This request is in regard to the additional data files submitted on July 30, 2009. Provide the SAS code to generate the following formats: visitnum, checked, yesno, exdose, nonetkn, pilltkn, exdiscrn, pga, qtfdur, qtfws.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
(: 301-796-9723/9713
Mail: Diana.Walker@fda.hhs.gov

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

From: Walker, Diana
Sent: Thursday, August 06, 2009 1:55 PM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Information Request/06Aug09
Importance: High

Dear Susan,

I have received a request for information from our review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please provide this information no later than August 12, 2009. If you can not provide the information on or before that date, please call me. Please submit the following items:

For clinical study c-2004-022-00, we have found the report of the study, but not the dataset. We require the dataset to do statistical analysis.

Provide a location within the submission for this dataset, or submit the dataset to the NDA.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

From: Walker, Diana
Sent: Monday, August 03, 2009 2:58 PM
To: Susan Franks
Subject: NDA 21-217 Exalgo/Clinical Information Request/03Aug09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

Section 5.2 includes a Tabular Listing of All Clinical Studies Included in this Submission and Ongoing Studies.

The following studies are listed in this tabulation, but are not included in the ISS Tabulation of Clinical Safety Studies (Module 5.3.5.3) or in Figure 1, p. 20 of the ISS.

DO-111
DO-112
D-51-PK
D-56-PK
D-73-PK
DO-115

The above studies were not discussed in the original NDA, nor were they listed in the pooled and non-pooled studies for the ISS for this submission. The final reports of the studies are included in the submission but the safety data is not selected in the ISS.

Please explain the rationale for why these studies were omitted in the ISS or provide additional information for clarification.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

From: Walker, Diana
Sent: Wednesday, July 29, 2009 11:56 AM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Clinical Information Request/29Jul09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items:

Please identify where in the submission a tabulation or summarization of all clinical studies into Phase 1, 2 or 3 can be found.
If this information is not already in the submission, provide such a table.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
OA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

'rom: Walker, Diana
Sent: Monday, July 27, 2009 4:47 PM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Statistical Information Request/27Jul09
Importance: High

Dear Susan,

I have received a request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items regarding **NMT 1077-301**:

The program file XEF.SAS uses the following SAS data files which have not been submitted: DIARY, QUEST, MEDDISP, and MEDRETN.
Provide these files with appropriate documentation.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

'ana L. Walker, Ph.D.
gulatory Project Manager
JA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6
NDA 21217	ORIG 1		DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

DIANA L WALKER
08/12/2009

Walker, Diana

rom: Walker, Diana
Sent: Friday, July 10, 2009 12:01 PM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Statistical Information Request/10Jul09
Importance: High

Dear Susan,

I have received a request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items regarding **NMT 1077-301**:

1. **The analysis of the primary endpoint submitted on July 7, 2009 , in response to an Information Request used pooled centers and a baseline score derived only from diary data.**

   - **Provide the code used to conduct the analysis, as well as an updated analysis data file which includes the recalculated baseline and pooled centers.**
   - **Explain why subjects 084014 and 084017 were excluded from the intent-to-treat set.**

Please contact me if you have any questions or need clarification on this request.

Regards,

na

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
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Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/17/2009 11:34:55 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Monday, July 06, 2009 12:46 PM
To: 'Susan Franks'
Subject: RE: CMC info and new CMC information request-06Jul09
Importance: High

Dear Susan,

I have received a request for clarification from our CMC review staff.

Clarify if the (b) (4), listed in the DMF (b) (4)' will be used for the (b) (4) for this NDA. If, so, to provide the name contact, phone number and FAX number at the site.

Please submit this information through the Gateway as soon as possible as with the information from the previous request. This information and the previous contact information is requested to be submitted through the Gateway this week if at all possible! Thank you.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
A/CDER/ODE II/DAARP
: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Susan Franks [mailto:Susan.Franks@premier-research.com]
Sent: Wednesday, July 01, 2009 1:55 PM
To: Walker, Diana
Subject: CMC info

Hi Diana,
Here is the information requested by the CMC reviewers for the sites. I assume this also needs to be submitted formally to the NDA? Let me know if any questions:

Drug Substance Manufacturing Site:
(b) (4)

oduct Manufacturing/Testing Site:
Jennifer Leopold
Director of Quality
ALZA Corporation

700 Eubanks Drive
Vacaville, CA 95688
Phone: 707-453-6579
: 707-453-6430
E-mail: jleopol1@its.jnj.com

Product Packaging Site

(b) (4)

Product Stability Testing

(b) (4)

Susan M. Franks, M.S.
Director, Regulatory Affairs
Premier Research Group
755 Business Center Drive
Suite 200
Horsham, PA 19044
ph: 215-907-1330 ext 1025

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/s/

Diana Walker
7/17/2009 11:33:57 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, July 01, 2009 8:21 AM
To: 'Susan Franks'
Subject: NDA 21-217/FDA CMC Information Request/01Jul09
Importance: High

Dear Susan,

Please submit the following information to your NDA as soon as possible, as without this information we will not be able to proceed with facilities inspections.

Provide as soon as possible:

1. The name and address of the drug substance manufacturer, (b) (4) to the NDA.

2. The contact names, telephone numbers and FAX numbers at all manufacturing facilities.

Regards,

na

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
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/s/

Diana Walker
7/17/2009 11:33:00 AM
CSO

Walker, Diana

'rom: Walker, Diana
Sent: Tuesday, June 30, 2009 9:21 AM
To: 'Susan Franks'
Subject: RE: NDA 21-217 Exalgo/Statistical Information Request #2/26Jun09
Importance: High

Dear Susan,

Our statistics reviewer has the following comments regarding your inquiry from the email below:

1. **Run the analysis using the method specified in the SPA, and include all of the code. We should be able to trace your results back to the tabulation data. This applies to the version 5 results also.**
2. **The subgroup analysis can be based on the final SAP. Again, you should include all of the code.**

Please contact me if you need further clarification on any of these points.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
'A/CDER/ODE II/DAARP
: 301-796-4029
ax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Susan Franks [mailto:Susan.Franks@premier-research.com]
Sent: Monday, June 29, 2009 3:46 PM
To: Walker, Diana
Subject: RE: NDA 21-217 Exalgo/Statistical Information Request #2/26Jun09

Hi Diana,

In response to question 2 below, would you be able to provide this response to the Statistical team and let us know whether additional analyses should be conducted:

The baseline NRS score was computed as the mean of the patient diary measurements in the week prior to randomization , which included Double-blind visit 1, as footnoted in Listing 16.2.6.1. The footnote 'c' in Table 15 on page 89 of the 301 CSR should read, "*Mean of the patient diary measurements in the week prior* to randomization and double-blind visit 1". The definition for baseline NRS is outlined in SAP version 5.0 submitted in the Complete Response. Neuromed recognizes that this is inconsistent with the definition outlined in version 2.0 of the SAP (that which was reviewed as part of the SPA process). Please advise as to whether a reanalysis using SAP version 2.0 is required. If so, should an analysis of the primary endpoint by age, race, and nder be conducted using the definition of baseline according to SAP version 2.0?

Many thanks,
Susan

Susan M. Franks, M.S.
ector, Regulatory Affairs
mier Research Group
755 Business Center Drive
Suite 200
Horsham, PA 19044
ph: 215-907-1330 ext 1025

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Friday, June 26, 2009 2:28 PM
To: Susan Franks
Subject: NDA 21-217 Exalgo/Statistical Information Request #2/26Jun09
Importance: High

Dear Susan,

I have received a second request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner. Please submit the following items regarding **NMT 1077-301**:

1. **Submit the SAS code used to create the analysis datasets and perform the efficacy analyses.**

2. **In a footnote to Table 15 in the Clinical State Report (p. 89), you state that the baseline pain intensity was the mean of "the patient diary measurements in the week prior to randomization". This is consistent with the final Statistical Analysis Plan. However, the paragraph that introduces Table 15 also references Listing 16.2.6.1, which has a footnote stating, "Baseline NRS score from patient diary and Double-Blind Visit 1." Clarify how the baseline NRS score was computed for the primary analysis.**

3. **We are not able to locate an analysis of the primary endpoint by age, race, and gender. Provide the location of this analysis in the NDA. If this analysis has not been submitted, perform the analysis and provide the results.**

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/17/2009 11:31:53 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, June 17, 2009 10:27 AM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Clinical Information Request/17Jun09
Importance: High

Dear Susan,

I have received a request for information from our Clinical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible, but no later than Tuesday, June 23, 2009, so that the review team is able to complete their review in a timely manner.

The Agency requires that CRFs be submitted for all deaths, SAEs and withdrawals due to adverse events. We have not been able to locate all of the above in the submission.

1. **Direct us to their location in the submission, or if not submitted, do so.**
2. **Submit patient narratives for all deaths and SAEs.**

Please contact me if you have any questions or need clarification on this request.

Regards,

Dina

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/17/2009 11:28:53 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Thursday, June 25, 2009 9:15 AM
To: 'Susan Franks'
Subject: NDA 21-217 Exalgo/Statistical Information Request/25Jun09
Importance: High

Dear Susan,

I have received a request for information from our Statistical review team for your NDA 21-217. Please submit the following to your NDA as soon as possible so that the review team is able to complete their review in a timely manner.

In the original statistical analysis plan (SAP), dated July 16, 2007, the primary analysis is an analysis of covariance with Week 12 pain intensity as the dependent variable, treatment and center as factors, and baseline pain intensity as the covariate. This SAP was included in a Special Protocol Agreement (SPA). Provide the location of this analysis in the NDA. Conduct the analysis and submit the results, if it has not already been provided in the NDA.

Please contact me if you have any questions or need clarification on this request.

Regards,

Diana

.na L. Walker, Ph.D.
.egulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/17/2009 11:30:45 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Lidia Mostovy/Knoll Pharmaceuticals
Phone Number: (973) 426-6019
Fax Number: (973) 426-6068

FROM: Judit Milstein

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7440 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 4-12-00

COMMENTS: Find enclosed the information requested by the reviewers. Thanks.

Please provide written documentation of how the electronic data sets provided in section 11 of the NDA are organized. Please include in your documentation the information necessary to examine or determine the following for each subject in studies 104/105/119 and 109:

Baseline diagnosis and analgesic treatment, including medication(s) and dose(s) and starting Dilauded dose.

Duration of stabilization in days

Duration of titration in days

Number and size of titration steps

Duration of treatment with final assigned treatment in days

Total duration of study participation in days (including time on treatment in the extension study) and status at study end (completed, withdrew) and reason for withdrawal

Amount and frequency of rescue medication used in each study period.

Use of rescue medication as required for determination of efficacy

Listing of adverse events, including days on treatment, visit number and study phase (stabilization, titration, treatment phase or open label extension) at time of onset, duration, severity resolution, and dose of medication and dose of rescue at time of onset. The information should include an explanation of how to determine who had an adverse event that began in studies 119, 104/105 and continued into the open label extenstion study.

Listing of concomitant medications, including days on treatment, visit number and study phase (stabilization, titration, treatment phase or open label extension) at time of onset, duration, severity, resolution and dose of medication and dose of rescue at time of onset.

Finally it would be most helpful if you could provide word processed versions of the final study reports for studies 104/105, 119, 109 the ISS and ISE and a desk copy of volume 179 (Section 11, data listings including annotated CRFs).

Provide the CMC section in electronic format.

Electronic Mail Message

Date: 2/9/00 12:06:30 PM
From: Thomas Permutt (PERMUTTT)
To: Debra Fong (FONGD)
Cc: Douglas Kramer (KRAMERD)
Subject: dilaudid info. request

The statistical review could be completed much more efficiently if the sponsor would be kind enough to provide an additional machine-readable data set. It should contain data from which Tables 18.0-18.5 in the report of study DO-119 can be easily computed, namely:

subject id
site
treatment group
age
race
sex
amount of breakthrough medication (endpoint)
amount of breakthrough medication (baseline)
number of doses of breakthrough medication (endpoint)
number of doses of breakthrough medication (baseline)
dose of study drug (by which breakthrough doses are normalized)

. single data set with these variables and other closely related ones that the sponsor feels would be useful would be most helpful. I have looked at the electronic submission, and I realize that it probably contains most of this information; but it does not seem to be documented in such a way that this critical information can be efficiently extracted. If the sponsor wants to tell me how to do that, that would be acceptable; but I imagine it will be less convenient on both sides than this small additional submission.

The data should be submitted in the form of a SAS version 5 transport data set so that it can be archived by the electronic document room.

Doug has additional needs for the medical review.

Tom

Electronic Mail Message

Date: 2/10/00 1:18:15 PM
From: Douglas Kramer (KRAMERD)
To: Cynthia McCormick (MCCORMICKC)
To: Thomas Permutt (PERMUTTT)
To: Debra Fong (FONGD)
Subject: NDA 21217 clinical data

Cynthia,
The current clinical data section is described in the attached along with basic information about what we would need to see for review purposes.

Doug

Information Request

As submitted the listings of the paper submission are inadequate to allow substantive review. The data are not tabulated in a manner that will allow verification of the sponsor's reports (examples: there is no link between data elements in the CRF and the data in the paper tabulations; subject numbers changed in the open label extension study and subjects cannot be traced back to their original data in the short term titration studies; study events are reported by date rather than by day of treatment and visit number; it cannot be determined whether the paper tabulations are complete; treatment group assignments for study 119 could not be located; tabulations of derived data from which the sponsor from which the sponsor would have directly made their final tables –by-patient by-visit summaries of study and rescue medication use, for example—cannot be located. A detailed table of contents for section 8 will also be required listing the volumes where individual listings can be found.

As an alternative to attempting to fix the paper submission, the sponsor's electronic data (for which annotated CRFs were included in section 11) was considered. This was also found to be inadequate for substantive review. Because the electronic data was easier to follow the types of deficiencies found in it are described in somewhat greater detail below. The same types of deficiencies were identified in the paper listings. **The deficiencies are such that it is not clear to me that they can be fixed and reviewed in the time remaining before a final filing decision must be made for this application.**

The following request pertains to all clinical studies in the NDA (104/105/119/109), to the safety data from pharmacokinetic studies and to the ISS and ISE. The following description of required data focuses on studies 104/105/119/109 because data sets from these studies have been provided and examined.

The sponsor should provide annotated CRFs describing the relationship between the data fields in the CRF and the data in the electronic data sets. Where data in the CRF is recorded as a numeric code, the code should be translated in the data set with a key provided on the annotated CRF (e.g. 0 on CRF = NO in data set, 1 on CRF=YES in data set, etc).

I have not been able to locate analytic data sets that will enable me to directly derive tables in the study reports, ISS and ISE. We will need to verify with the sponsor whether the electronic data includes analytical data sets that can be used to produce directly the tables in their NDA. If not, analytical data sets should be requested as well in lieu of the SAS programs and documentation necessary to convert existing data sets to analytical data sets. The sponsor should provide a description of analytical data sets used to produce the tables in the NDA and how

to produce those tables directly from the data sets provided. This should include documentation of calculation methods for all derived variables and summary variables.

In providing this information, we should specifically ask the sponsor to make sure we can directly do the following:

- Link data from subjects in study 109 to their corresponding data in studies 104, 105 or 119. (The subject numbers in the electronic data set seem to have changed at entry into the open label study.)

- Determine (as appropriate) for any visit in any study the baseline morphine equivalent dose, the starting titration dose, the ending titration dose, the current dose (of study drug, rescue medication and total), the final dose, the number of the current titration step, the length of the titration period, the size of titration doses or rescue medication use for each patient.

- Determine the total number of days on treatment with dilaudid CR (both for studies 104/105/119 individually and for study 104/105/119 plus study 109).

- Determine for any study the timing of major study events for each subject (including dose changes, adverse events, changes in physical examination, concomitant medication use and study termination) by day of treatment, visit number and dose of study medication and rescue medication taken at the time of the event. It should be possible to determine the dose of medication taken both in milligrams and in any other format used in the sponsor's analyses.

- Locate the treatment group assignment (e.g. IR, CR, ½ CR) for study 119. The sponsor should direct us to the location of this information if it is submitted or provide it.

We should note to the sponsor that coding of the same information (e.g. visit number, dose) should be consistent between data sets for the same study and across studies as well. We should also request that units on numeric data be included in separate data fields such that actual numeric data can be used directly without having to strip units off the values.

In designing the appropriate data sets, it would be helpful if the sponsor could include basic demographic information (including baseline analgesic use, morphine equivalent of baseline analgesic use, diagnosis, age, gender, weight, pain type, cancer type) in each file of analytical data to reduce the amount of data manipulation necessary in analyzing the data. Note that the type and organization necessary is well described in the agency's guidance documents on electronic submissions.

As the submission stands, it cannot be substantively reviewed, either on paper or electronically. **The deficiencies are such that it is not clear to me that they can be fixed and reviewed in the time remaining before a final filing decision must be made for this application.**

Walker, Diana

From: Greeley, George
Sent: Thursday, November 05, 2009 10:30 AM
To: Walker, Diana
Cc: Stowe, Ginneh D.
Subject: NDA 21-217 Exalgo

Importance: High

Hi Diana,

The Exalgo (Oros Hydomorphone or hydromorphone HCL) partial waiver/deferral and plan was reviewed by the PeRC PREA Subcommittee on October 14, 2009.

The Division recommended a partial waiver for pediatric patients 0<2 years because studies are impossible or highly impractical because there are too few children with disease/condition to study and a deferral from 2 years to 16 years of age because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

It is also recommended by the PeRC that the sponsor develop and ER formulation that could go down to age 2.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	ALZA CORP	Exalgo (hydromorphone HCl) 8/12/16

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/s/

DIANA L WALKER
03/04/2010

Electronic Mail Message

Date: 2/9/00 8:13:12 AM
From: Michael Klein (KLEINM)
To: Debra Fong (FONGD)
Subject: NDA 21-217 Dilaudid CR Tablet

Debra:

I looked over the 6 page narrative on Drug Abuse and Overdose Information from the NDA.

The sponsor has not requested a rescheduling of the product from CII. However, the sponsor makes the statement that this product has less abuse potential than the immediate release product. Seven cases from the clinical development program in which there was development of a withdrawal syndrome are listed in TABLE 1 (page 2). Table 2 lists 4 overdose cases during clinical development. The safety portion of the medical review should address the frequency of these events and the specific details about their occurrence. If the sponsor wants to state in the labeling that this product has less abuse potential, it would have to be supported with comparable data presented for the immediate release products. I doubt that such data exists, however.

Mike

DILAUDID CR
NDA 21-217
PM: J. MILSTEIN

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the ADA application: **YES** **NO**

STATISTICAL:

(1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the statistical section of the NDA legible so that substantive review can begin? ✓

(4) On its face, do there appear to be at least two adequate and well-controlled studies in the application? ✓ 1 study, apparently by agreement, seemingly failed

(5) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? ✓

(6) Are all data sets for pivotal efficacy studies "complete for all indications (infections) requested? ✓ no intermediate data set — sponsor says will provide

(a) Line listings by-Center

(b) Intermediate analysis summary tables

(c) Pathogen listing

(d) Adverse events listing by center

(e) Lost subject/patient tables by reason, time of loss, and center

STATISTICAL: **YES** **NO**

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? ✓

(8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not. ✓

Reviewing Statistician Date 2/29/00

Supervisory Statistician Date

8 pp withheld in full immed. after this page as (b)(4) CCI/TS.

Electronic Mail Message

Date: 2/8/00 3:45:07 PM
From: Venkata Ramana Uppoor (UPPOORR)
To: Shiew-Mei Huang (HUANGS)
Cc: Tien-Mien Chen (CHENT)
Cc: Debra Fong (FONGD)
Subject: re: Dilaudid CR NDA

Hi Shiew-Mei,

We have an NDA in HFD-170 for Dilaudid CR (NDA 21-217). This NDA contains pivotal bioequivalence studies between the clinical and to-be marketed tablet formulation. I am not sure how this fits into the DSI priorities (Vish's group) for inspection. Please forward this to his group as appropriate. I think one of the bioequivalence studies, conducted on the highest strength will be a good study to inspect. This NDA came in December 1999, and the reviewers have decided to complete reviews in June/July of 2000, therefore any inspection has to be completed by that time.

Please forward this as appropriate to Wes Metz (who used to be the coordinator for all inspection requests) and DSI.

Thanks and appreciate a quick response!
Ramana Uppoor