CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-217s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Date:	March 24, 2010
To:	Bob Rappaport, MD, Director Division of Division of Anesthesia and Analgesia Products (DAAP)
Through:	Claudia Karwoski, PharmD, Director Division of Risk Management (DRISK)
From:	Mary Dempsey, BS, Coordinator Risk Management Programs, DRISK Jeanne Perla, PhD, Risk Management Analyst
Subject:	Review of New Supplement for NDA 021217 Exalgo; Prior Approval Supplement; Proposed REMS Modification; REMS Assessment
Drug Name(s):	Exalgo (hydromorphone HCl) Extended-Release Tablets
Application Type/Number:	NDA:021217
Applicant/sponsor:	Mallinckrodt Inc, a Coviden company
OSE RCM #:	2010-600

1. Background

The Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Risk Management (DRISK) review the Exalgo proposed Risk Evaluation Mitigation Strategy (REMS) Modification for New Drug Application (NDA 021217) submitted by Mallinckrodt Inc. on March 12, 2010.

Exalgo (hydromorphone HCl) Extended-Release Tablets which contains a Risk Evaluation and Mitigations Strategy (REMS) was approved March 1, 2010.
The REMS includes the following elements:

- Medication Guide
- Elements to Assure Safe Use
    - Healthcare Providers who prescribe Exalgo will receive training
    - Within 60 days of approval of Exalgo, a Dear Healthcare Professional Letter to include the EXALGO Healthcare Professional Education Program Kit will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians.
- Timetable for Submission of Assessments

A letter dated March 4, 2010 from Alza notified the FDA of a change in ownership and stated that Alza Corporation transferred ownership to Mallinckrodt Inc, a Coviden company. This supplemental new drug application provides for changes to the company name, address, and logo in the approved REMS to reflect the Transfer of Ownership of NDA 021217 from Alza to Mallinckrodt Inc, which was effective March 4, 2010. It also includes a modification to remove the (b) (4) to the approved Exalgo REMS and Medication Guide.

2. Material Reviewed

- March 1, 2010 Exalgo REMS approval
- March 4, 2010 Transfer of Ownership letter
- March 12, 2010 Proposed REMS Modification
- March 15, 2010 REMS Assessment
- March 23, 2010 amended proposed REMS to remove the (b) (4)

3. Proposed REMS Elements

The Exalgo March 12, 2010 submission and the March 23, 2010 Amendment provides the REMS, REMS Supporting Documents and associated 'educational tools' for Exalgo due to the transfer of the NDA from Alza to Mallinckrodt, Inc. The submission has the following components:

1. REMS Proposal
2. REMS Supporting Document
3. Exalgo Medication Guide
4. Prescriber Introductory Letter
5. Print Educational Materials: Healthcare Professional Education Program Kit
6. Print Educational Materials: Exalgo Essential Information Form
7. Print Educational Materials: Exalgo Prescribing Brochure

4. Discussion and Conclusion

DRISK performed an comparison of the March 12, 2010 submitted proposed REMS and Medication Guide and the March 23, 2010 amended REMS, to remove the (b) (4) ,to the approved Exalgo REMS and Medication Guide and found them to be identical.

The only changes to the REMS and Supporting Documents approved March 1, 2010 is that the Alza references are deleted and replaced with the Mallinckrodt Inc, a Covidien company name, address, and logo.

5. Recommendation

Approve the REMS Modification submitted on March 12, 2010 as amended March 23, 2010.

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

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03/24/2010

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03/24/2010
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 1, 2010
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead:** Jeanne Perla, Ph.D., Risk Management Analyst **Team Members:** **DRISK** Marcia Britt, Ph.D., Health Education Reviewer Brian Gordon, MA, Social Science Reviewer Sharon Mills, BSN, RN, CCRP, Patient Product Information Reviewer Acting Team Leader Gita Toyserkani, Pharm.D., MBA, Acting Team Leader **Division of Pharmacovigilance II** Afrouz Nayernama, Pharm.D., Safety Evaluator **Division of Medication Error Prevention and Analysis** Kristina Arnwine, Pharm.D., Safety Evaluator **Division of Drug Marketing, Advertising and Communication** Mathilda Fienkeng, Pharm.D., Regulatory Review Officer Twyla Thompson, PharmD, Regulatory Review Officer **Office of Compliance Division of Risk Management and Surveillance** Agnes Plante, BSN, RN, Consumer Safety Officer
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	EXALGO (Hydromorphone HCL) Extended Release (ER)
Application Type/Number:	NDA 21-217
Applicant/sponsor:	ALZA Corporation
OSE RCM #:	RCM: 2009-1108

EXECUTIVE SUMMARY

EXALGO (Hydromorphone HCL) ER is an opioid analgesic with the proposed indication for the management of moderate to severe chronic pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. The Sponsor voluntarily submitted a proposed Risk Evaluation and Mitigation Strategy (REMS) on May 22, 2009. In accordance with section 505-1 of the FDCA, the Agency determined that a REMS is necessary for EXALGO to ensure that the benefits of the drug outweigh the risks of abuse, misuse, and overdose, as well as the risk of use of EXALGO in non-opioid tolerant individuals. The Sponsor was officially notified of this requirement on February 12, 2010.

The Agency has been considering REMS elements that should be implemented for a number of opioid products, including modified-release opioids, to address the risks of abuse, misuse, and overdose. A class REMS for long-acting and high potency opioids is also being considered. Until the Agency has determined the elements or possibly a class-wide REMS, DAARP with input from OSE, has decided that an interim REMS for long-acting and high potency opioids will be required as these products are approved.

The Sponsor has submitted an interim REMS to address the risks of abuse, misuse, overdose, and addiction. The REMS includes a Medication Guide, Element to Assure Safe Use, specifically a plan to ensure Healthcare providers who prescribe EXALGO will receive training under 505-1(f)(3)(A),and a timetable for submission of assessment of the REMS. We find the proposed REMS submitted on February 25, 2010 to be acceptable.

Once the elements of the class-wide opioid REMS are determined, the Sponsor will be notified to resubmit a REMS incorporating these elements, as was conveyed to the Sponsor in the February 12, 2010 Information Request letter.

1 BACKGROUND

1.1 INTRODUCTION

The proposed indication for EXALGO is for the management of moderate to severe chronic pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. EXALGO Tablets are manufactured in 8 mg, 12 mg, 16 mg, and 32mg dosage strengths. The Sponsor has agreed not to market the 32mg strength and the Agency will not approve the 32mg strength at this time. EXALGO will be contraindicated in the management of acute or postoperative pain and is not intended for use as an as needed analgesic. EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed or dissolved tablets can lead to rapid release and absorption of a potentially fatal dose of hydromorphone. The clinical review of the clinical trials did not identify any unexpected adverse events, but did find the typical opioid-related adverse events.

A joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory committee was held on September 23, 2009. The joint committee was asked to provide guidance regarding whether EXALGO is likely to be less susceptible to abuse and misuse than currently marketed extended-release opioids, and if EXALGO should be included with the class opioid REMS or have a

REMS that is specific to EXALGO. The advisory panel did not vote on any specific questions but provided advice in the form of discussions. The panel supported the sponsor's proposed REMS, along with a phased marketing rollout, starting with the lowest dosage strengths and targeting specific medical specialties and patient types, such as those with cancer.

1.2 REGULATORY HISTORY

During the review of this NDA, the Agency made a determination that long-acting and high potency opioids require a REMS to address the risks of abuse, misuse, and overdose.

On February 18, 2009, a General Correspondence Letter was sent to the Sponsor informing them that a class REMS for modified-released opioids would be implemented in the future. Until such a REMS was approved, Neuromed Pharmaceuticals was to submit a REMS that comprised of a Medication Guide, a Communication Plan, and a timetable for submission of assessments. The letter stated that once the elements of the class-wide REMS were determined, the sponsor would be required to submit a REMS incorporating these elements.

On May 22, 2009 (and amended on November 17, 2009), Neuromed submitted a proposed REMS in response to the general correspondence letter. After reviewing the proposed REMS and upon further consideration, the Agency determined that a Medication Guide and communication plan would not be adequate to ensure adequate training of healthcare providers to address the risks of abuse, misuse, and overdose, as well as the risk of use of EXALGO in non-opioid tolerant individuals. Therefore, on February 12, 2010, Neuromed was notified that the REMS for EXALGO (hydromorphone HCl) must contain an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), to ensure that the benefits of EXALGO (hydromorphone HCl) outweigh the risks.

On February 12, 2010, the Agency was notified of the change of ownership of the NDA 21-217 (EXALGO) from Neuromed to ALZA Corporation. ALZA submitted an amended REMS on February 17, 2010 and subsequently the final REMS proposal on February 25, 2010.

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION SOURCES

1. General Correspondence Letter sent February 18, 2009
2. Proposed REMS submitted May 22, 2009
3. Proposed REMS amendment, submitted November 17, 2009
4. REMS notification letter sent February 12, 2010
5. Proposed REMS amendment (in response to REMS notification letter), submitted February 17, 2010
6. Proposed REMS amendment, with final REMS proposal submitted February 25, 2010

2.2 ANALYSIS TECHNIQUES

The submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and the elements outlined in the REMS Notification Letter, as well as responsiveness to comments submitted to the Sponsor as part of the ongoing review.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Safety concerns identified by the sponsor, DAARP and OSE are the potential for abuse, misuse, overdose, and addiction of EXALGO as well as the risk of use of EXALGO in non-opioid tolerant individuals.

3.2 PROPOSED REMS

The February 25, 2010 final proposed REMS submission contains the following:

3.2.1 Goals:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose and addiction of EXALGO.
2. To inform patients and healthcare professionals about the safe use of EXALGO

3.2.2 Medication Guide (MG)

A Medication Guide will be dispensed with each EXALGO prescription in accordance with 21 CFR§208.24. The following additional measures will be instituted:

1. Medication Guides will be included in the primary and secondary packaging of the commercial product.
2. One (1) Medication Guide will be affixed (spot glued) to each bottle of EXALGO
3. Additional Medication Guides (48) will be provided with each carton containing 12 bottles of EXALGO, partial cases will include four additional Medication Guides per bottle.
4. The Medication Guide also will be available through the product website (www.exalgo.com), the EXALGO REMS website (www.exalgorems.com) or through the Sponsor's toll-free Product Monitoring Department number at 1-866-377-3485.
5. The Medication Guide also will be distributed with the EXALGO REMS Healthcare Professional Education Program Kit as part of the prescribing program.

3.2.3 Elements to Assure Safe Use

1) Healthcare Provider Training.
    a. ALZA will ensure that training will be provided to healthcare providers who prescribe EXALGO. To become trained, each prescriber will be provided with the materials in the EXALGO REMS Healthcare Professional Education Program Kit.

    The training addresses the following:
        i. Proper patient selection

ii. Appropriate EXALGO dosing and administration

iii. General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction

iv. The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including EXALGO

v. The risks of EXALGO including:

1) The risk of overdose caused by exposure to an essentially immediate-release form of hydromorphone due to broken, chewed, crushed, or dissolved EXALGO

2) The risk of addiction from exposure to EXALGO.

3) The risk of overdose with use in opioid non-tolerant individuals

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

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

b. ALZA will ensure that within 60 days of approval of EXALGO, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of EXALGO as well as the need to complete the EXALGO REMS Education Program. This letter will also be available on the exalgorems.com website for 1 year.

c. The mailing will also include the EXALGO Healthcare Professional Education Program Kit which will consist of the following:

i. A copy of the Prescribing Information (PI);

ii. The Medication Guide;

iii. The EXALGO Prescribing Brochure;

iv. The EXALGO Essential Information Form.

d. Additional printed educational materials will be made available through field- force distribution and the toll-free Product Monitoring Department number at 1-866-377-3485.

e. The educational materials will be available for download at **www.exalgorems.com**.

f. ALZA will maintain a list of all prescribers that have completed the EXALGO REMS Education Program.

g. Prescribers will be re-trained, including review of the educational material and completion of the EXALGO Essential Information Form, every two years or following substantial changes to the EXALGO REMS. Substantial changes may include, changes in the EXALGO Full Prescribing Information, EXALGO Medication Guide, or EXALGO REMS that require substantial modification of the educational materials.

The following materials are appended to the REMS:

- Dear Healthcare Professional Letter
- EXALGO REMS Website
- EXALGO REMS Healthcare Professional Education Program Kit
  - Prescribing Information
  - Medication Guide
  - EXALGO Essential Information Form
  - EXALGO Prescribing Brochure

3.2.4 Implementation System

Because EXALGO can be approved without the Elements to Assure Safe Use described under 505-1(f)(3)(B), (C), and (D) of the Act an implementation system is not required.

3.2.5. Timetable for Submission of Assessments

ALZA will submit REMS Assessments to FDA every 6 months for the first year from the date of approval of the REMS, 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 will conclude no earlier than 60 days before the submission date for that assessment time interval. ALZA will submit each assessment so that it will be received by FDA on or before the due date.

The REMS Assessment Plan was summarized in the REMS Supporting Document and will be included in the approval letter. It will include at a minimum:

1. An evaluation of patients' understanding of the serious risks of EXALGO.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4. A report on the status of the training program for healthcare providers.

5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with EXALGO (for example, through surveys of healthcare providers).

6. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

8. An analysis to evaluate Exalgo (hydromorphone HCl) utilization patterns including use in non-opioid tolerant patients.

9. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

The Sponsor did not submit the survey instruments or methodologies. Without the survey instruments and methodologies there is insufficient information to complete a review of the patient and prescriber surveys. The Sponsor was informed to submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of EXALGO at least 90 days before the evaluation will be conducted. The submission should include all methodologies and instruments that will be used in the evaluations. General comments about what should be included in the patient and prescriber methodologies and survey instruments were emailed to the Sponsor (Appendix A) on February 25, 2010.

4 DISCUSSION AND CONCLUSION

An interim REMS will be implemented by the Sponsor until a class-wide opioid REMS has been approved. The proposed REMS dated February 25, 2010 contains the required REMS elements which includes a Medication Guide, element to assure safe use, and a timetable for submission of assessments.

The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals. The Sponsor did not submit the patient and prescriber survey instruments or methodologies; however, this information does not need to be submitted for FDA review prior to approval of the REMS. The Sponsor was informed to submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of EXALGO at least 90 days before the evaluation will be conducted. Below we provide preliminary comments to the Sponsor regarding the planned patient and prescriber surveys. Please consult DRISK request once the survey instruments and methodologies have been submitted by the Sponsor.

Based on our current understanding of the risks of EXALGO, DRISK believes that a REMS comprised of these components is appropriate until a class-wide opioid REMS is established.

APPENDIX A: Comments on EXALGO Patient and Prescriber Surveys

Submit for review the detailed plans that will be used to evaluate patients' and prescribers' 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 the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodologies and instruments that will be used in the evaluations.

1. Recruit respondents using a multi-modal approach. For example, patients might be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
2. Explain how non-respondent follow-up or reminders will be completed and the planned frequency of the non-respondent follow-ups.
3. Explain how incentive or honorarium will be offered and the intended amount.
4. Explain how sites will be selected.
5. Submit for review any recruitment advertisements.
6. Define the sample size and confidence interval associated with that sample size.
7. Define the expected number of prescribers and patients to be surveyed, and how the samples will be determined (selection criteria)
8. Explain the inclusion criteria; that is, who is an eligible respondent. For example, a *patient* respondent might be:
    - Age 18 or older
    - Currently taking Exalgo or have taken in past 3 months
    - Not currently participating in a clinical trial involving Exalgo
9. Submit any screener instruments, and describe if any quotas of sub-populations will be used.
10. Explain how the surveys will be administered and the frequency of the surveys.
11. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy patient population. For example, surveys could be completed online, in writing or by mail, over the phone, or in person.
12. Explain how surveyors will be trained.
13. Explain controls used to compensate for the limitations or bias associated with the methodology
14. The patient sample should be demographically representative of the patients who use Exalgo.
15. The prescriber sample should be demographically representative of the healthcare providers who prescribe or administer Exalgo.

16. If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically
17. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
18. Potential respondents should be told that their answers will not affect their ability to receive or take (patients) or prescribe (prescribers) Exalgo, and that their answers and personal information will be kept confidential and anonymous.
19. Respondents should not be eligible for more than one wave of the survey.
20. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
21. Data may be stratified by any relevant demographic variable, and presented in aggregate. We encourage you to submit with your required assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

With regard to the patient survey instrument:

22. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating patients' knowledge of the serious risks associated with and safe use of Exalgo. The assessment is not to evaluate consumer comprehension of the Medication Guide.
23. Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
24. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
25. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
26. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Exalgo?" section of the Medication Guide
27. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
28. The order of the multiple choice responses should be randomized on each survey.
29. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide.

Demographic questions should be collected last or as part of any screener questions.

30. Respondents should not have the opportunity or ability to go back to previous questions in the survey if the survey is conducted by telephone or online.
31. Explain if and when any education will be offered for incorrect responses.
32. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
33. Just prior to the questions about receipt of the Medication Guide, include text explaining what is a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with Exalgo. The Medication Guide is a paper handout that contains important information about the risks associated with use of Exalgo and how to use Exalgo safely. Medication Guides always include the title "Medication Guide".

34. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

a. Who gave you the Medication Guide for Exalgo? (Select all that apply)
    a) My doctor or someone in my doctor's office
    b) My pharmacist or someone at the pharmacy
    c) Someone else - please explain: _____
    d) I did not get a Medication Guide for Exalgo

b. Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

c. Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

d. Did someone offer to explain to you the information in the Medication Guide?
    - Yes, my doctor or someone in my doctor's office
    - Yes, my pharmacist or someone at the pharmacy
    - Yes, someone else – please explain:

      _____
    - No

e. Did you accept the offer? Yes or No

f. Did you understand the explanation that was given to you?
    - All,
    - Most,

- Some,
- None

g. Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

With regard to the prescriber survey instrument:

35. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating prescribers' knowledge of the serious risks associated with and safe use of Exalgo. The assessment is not to evaluate prescribers' comprehension of the educational materials.
36. Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) prior to taking the survey.
37. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
38. The prescriber knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.
39. Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
40. The order of the multiple choice responses should be randomized on each survey.
41. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.
42. Respondents should not have the opportunity or ability to go back to previous questions in the survey if conducted by telephone or online.
43. Explain if and when any education will be offered for incorrect responses.
44. Use the following (or similar) questions to assess receipt and use of the educational materials.

a. Prior to today, which of the following were you aware of or received with regard to Exalgo? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	□	□

Medication Guide	□	□
Dear Healthcare Provider Letter	□	□
Exalgo Prescribing Brochure	□	□
Exalgo REMS Healthcare Professional Education Program Kit	□	□
Something else - please explain:	□	□
None of the above	□	□

b. Did you read the Full Prescribing Information?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Exalgo Full Prescribing Information

c. Did you read the Medication Guide?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Exalgo Medication Guide

d. Did you read the Dear Healthcare Provider Letter?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Exalgo Dear Healthcare Provider Letter

e. Did you read the Exalgo Prescribing Brochure?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Exalgo Prescribing Brochure

f. Do you have any questions about any of the educational materials related to Exalgo? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

Please let us know if you have any questions.

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/

JEANNE P PERLA
03/01/2010

CLAUDIA B KARWOSKI
03/01/2010
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

M E M O R A N D U M

DATE: March 1, 2010

TO: File, NDA 21217 EXALGO (hydromorphone HCl) 8-, 12-, and 16-mg Extended-Release Tablets

From: Sharon Hertz, M.D.
Deputy Division Director

Through: Bob Rappaport, M.D.
Division Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for EXALGO (hydromorphone HCl) to ensure that the benefits of the drug

outweigh its risks of abuse, misuse, and overdose, as well as the risk of use of EXALGO (hydromorphone HCl) in non-opioid tolerant individuals.

In reaching this determination we considered the following:

A. The indication for the formulation in EXALGO (hydromorphone HCl), management of moderate to severe pain in opioid-tolerant patients when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, could result in use of the product in millions of patients.
B. Moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time is a fairly serious condition, particularly for those patients who have chronic pain due to etiologies that are unlikely to improve.
C. EXALGO (hydromorphone HCl) is an extended-release product. Other alternatives currently available, oral extended-release opioid products, contain oxycodone, morphine or oxymorphone. It is also important to note that patients respond differently to different opioid drug substances and some patients develop tolerance to an opioid after chronic exposure. Physicians use a technique known as "opioid rotation" whereby they switch patients from one opioid to another if patients develop tolerance and cannot get adequate pain relief from any given opioid. Therefore, having different opioids available as modified-release formulations provides important pain relief options for these patients.
D. The expected duration of treatment with the drug will be from weeks to months or longer.
E. In addition to postmarketing reports of serious events including death, respiratory depression, CNS depression, and abuse associated with hydromorphone hydrochloride and other marketed extended release opioid products, EXALGO (hydromorphone HCl) has been associated with various other adverse effects including severe hypotension, gastrointestinal tract reactions such as nausea and vomiting, hypersensitivity reactions including in patients sensitive to sulfites, and the known potential to elevate intracranial pressure and biliary tract pressure.

F. EXALGO (hydromorphone HCl) is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for EXALGO (hydromorphone HCl). FDA has determined that EXALGO (hydromorphone HCl) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of EXALGO (hydromorphone HCl) . FDA has also determined that EXALGO (hydromorphone HCl) is a product for which patient labeling could help prevent serious adverse events and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, EXALGO (hydromorphone HCl).

The elements of the REMS will be a Medication Guide, elements to assure safe use, specifically training for healthcare providers as described under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS.

_____
Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products

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/

SHARON H HERTZ
03/01/2010

BOB A RAPPAPORT
03/01/2010

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** February 24, 2010
EXALGO (hydromorphone HCl) extended-released tablets	21-217	**Comment Set # [3]**
DRISK Scientific Lead: Jeanne Perla, Ph.D., Risk Management Analyst		**Reviewers:** DRISK Marcia Britt, Ph.D., Regulatory Health Specialist Gita Toyserkani, Pharm.D. Acting Team Leader DDMAC Mathilda Fienkeng, PharmD, Regulatory Review Officer
RCM #: 2009-1108		

Materials Reviewed dated February 17, 2010
EXALGO proposed REMS
EXALGO supporting document
Educational materials:

- Dear Healthcare Professional Letter (DHCPL)
- EXALGO Essential Information Form
- EXALGO Prescribing Brochure
- EXALGO REMS Webpage

Introduction:
On February 12, 2010 Neuromed received a REMS notification letter stating that a Medication Guide and Communication Plan would not be adequate to ensure adequate training of healthcare providers to address the labeled risks and to prevent the occurrence of serious adverse events associated with those risks. Neuromed was informed that the REMS for EXALGO must contain a Medication Guide, an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS, to ensure that the benefits of EXALGO outweigh the risks. Neuromed submitted a revised REMS February 17, 2010.

Below are comments from the Division of Risk Management (DRISK) and the Division of Drug Marketing, Advertising and Communication (DDMAC) on the proposed REMS for EXALGO (hydromorphone HCl) extended-release.

Comments to be Communicated to the Sponsor

REMS
A. General Comments:

- See the appended EXALGO REMS document for track changes corresponding to comments below. **(Appendix A)** We have also provided a clean version of REMS document with the Agency's changes accepted. (Appendix B)
- Change all references from "sponsor" to Alza or Neuromed
- Change Neuromed to Alza where appropriate
- The REMS Supporting Document must reflect the below changes to be consistent with the REMS document.

A. Goals

The Goals have been reviewed and found to be acceptable. We have minor editorial revisions to the second Goal.

B. Medication Guide

- The Medication Guide has been reviewed and found to be acceptable.
- We find your plan to distribute the Medication Guide acceptable.
- We have minor editorial revisions to this section of the REMS document.
- Remove the EXALGO (b) (4) the Medication Guide should serve as the key patient education tool.

C. Communication Plan

We are not requiring a communication plan as part of the approved REMS (b) (4) moved to the elements to assure safe use section of the REMS. See comments below. The Dear Pharmacist Letter and Dear [Medical or Pharmacy] Association Letters can be sent out but will not be part of the REMS. We suggest that you consider our comments on the DHCP Letter for these letters.

D. Elements to Assure Safe Use

1. Dear Healthcare Professional (DHCP) Letter

Refer to the appended DHCP Letter with track changes. Most of the following issues are addressed in the version with tracked changes **(Appendix C)**.

i. The letter must include detailed instructions for accessing the required educational material.

ii. The letter presents the most commonly reported adverse events on page three while the boxed warning is presented on page four, after the signature line. This presentation minimizes the risks being communicated. The most serious information should be presented first in a manner consistent with the PI.

2. Remove the (b) (4)

3. Prescribing Brochure

Refer to the appended Prescribing Brochure with track changes. Most of the following issues are addressed in the version with tracked changes **(Appendix D)**.

i. The Prescribing Brochure includes the claim (emphasis added), (b) (4) [redacted] The statements have been deleted from the Prescribing Brochure. (see tracked changes)

ii. The proposed Prescribing Brochure presents the boxed warning or information from the boxed warning at the end of the brochure, thus minimizing the risks associated with EXALGO. Move this section to the front of the brochure. Remove the title (b) (4) [redacted]

iii. Throughout the proposed REMS materials, the boxed warning presented is inconsistent with the proposed PI. Specifically, they omit the sub-headers, "Potential for Abuse", "Proper Patient Selection", and "Limitations of Use". Revise the material placing the statement 'see the full prescribing information, boxed warning' before the boxed warning shown in the documents which is consistent with the boxed warning in the highlight section of the PI.

4. Essential Information Form See track changes **(Appendix E)**.
   i. The statement **"Completion of this form does not affect your ability to prescribe Exalgo."** was added to the top of the form.
   ii. "Date the form was completed" was added after prescriber information

5. EXALGO REMS webpage
   i. The sponsor should provide a webpage specifically for the Exalgo REMS. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a direct link (with equal prominence to efficacy claims and information) off the main product website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The webpage should not be a means to promote EXALGO or any other Sponsor product. Only this separate webpage and/or link will be considered a component of the REMS.

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

   iii. The Education Resource Page lists informational and training pieces that are not components of the Exalgo REMS. (b) (4) [redacted] Remove from the REMS webpage.

iv. The Web Shots include a section titled "Important Safety Information" (ISI), which presents the boxed warning for Exalgo. FDA notes that the boxed warning does not constitute a complete ISI for Exalgo and may minimize the risks associated with the product. The heading (b) (4) [redacted] ," should be eliminated.

E. REMS Supporting Document:

The following information needs to be included in your REMS Supporting Document under "Information Needed for Assessment:"

1. An evaluation of patients' understanding of the serious risks of EXALGO.

2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

4. A report on the status of the training program for healthcare providers.

5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with EXALGO (for example, through surveys of healthcare providers).

6. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

8. An analysis to evaluate EXALGO utilization patterns including use in non-opioid tolerant patients.

9. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

F. General Comments:

1. 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.

2. 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.

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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/

JEANNE P PERLA
03/02/2010

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** November 13, 2009
Exalgo (hydromorphone HCl) extended-released tablets	21-217	**Comment Set # [2]**
DRISK Scientific Lead: Jeanne Perla		**Reviewers:** DRISK Jeanne Perla PhD, Risk Management Analyst Marcia Britt PhD, Regulatory Health Specialist Mary Willy PhD, Deputy Director DDMAC Mathilda Fienkeng, PharmD, Regulatory **DPV** Afrouz Nayernama PharmD, Safety Evaluator
RCM #: 2009-1108		

Materials Reviewed all dated November 2, 2009:
Exalgo proposed REMS
Exalgo supporting document
Educational materials:

- Prescriber Program Brochure
- Prescriber Introductory Letter
- Pharmacy Introductory Letter
- Association Introductory Letter

The comments below are Office of Surveillance and Epidemiology's (OSE's) review of the proposed REMS for Exalgo (hydromorphone HCl).

This review includes revisions of the proposed REMS, Information Letters to the Healthcare Providers, Pharmacist and Professional Associations, and Guide for Healthcare Providers. See attached track changes

General comments to Sponsor

A. Goals

The Goals have been reviewed and found to be acceptable. No revisions are needed.

B. Comments about the Medication Guide

The Medication Guide has been reviewed and found to be acceptable.

C. Communication Plan

1. The Communication Plan has been reviewed and found to be generally acceptable.
2. Insert the following timeframe for the communication plan:
   In accordance with the United States federal Food, Drug, and Cosmetic ACT (FDCA) 505-1(e)(3), Mallinckrodt will execute a communication plan to HCPs to support implementation of Exalgo REMS for one year following approval of the NDA for Exalgo.
3. Ensure that the boxed warning is identical to the approved labeling boxed warning.
   See REMS tract changes

C.1 Specific Comments for Prescriber, Pharmacist, Association, Pain Care Center of Excellence and Compendia Letters

Prescriber Brochure

1. FDA finds the prescriber brochure generally letter acceptable.
2. The health education reviewer contends that the brochure contains much of the information already provided in the Prescribing Information. DRISK recommends shortening the document to include highlights of important safety information. Prescribers should rely on the Prescribing Information as the main source of safety information for Exalgo.
3. Change definition of opioid tolerant to "Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg transdermal fentanyl /hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oxymorphone /day, or an equianalgesic dose of another opioid, for 1 week or longer. "
4. Paginate the brochure.
5. See attached revised brochure

Dear Healthcare Provider letter

1. FDA finds the HCP letter generally acceptable.
2. change definition of opioid tolerant to "Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg transdermal fentanyl /hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oxymorphone /day, or an equianalgesic dose of another opioid, for 1 week or longer. "
3. The reference to the Medication Guide at the bottom of page 2 of the letter does not instruct healthcare providers to give each patient a Medication Guide. Please add this statement to the letter.
4. Remove [redacted] (b) (4)
5. See attached revised letter

Dear Pharmacist Letter

1. FDA finds the pharmacist letter acceptable.

2. Change definition of opi oid tolerant to “Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg transdermal fentanyl /hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oxymorphone /day, or an equianalgesic dose of another opioid, for 1 week or longer. “
3. Remove (b) (4)
4. See attached revised letter

Dear Association Letter

1. FDA finds the Association letter generally acceptable.
2. Change definition of opioid tolerant to “Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg transdermal fentanyl /hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oxymorphone /day, or an equianalgesic dose of another opioid, for 1 week or longer. “

See attached revised letter

Supporting Document

1. Table of Content 3.a. remove the word (b) (4)
2. In 3.a
   - remove the word (b) (4)
   - Educate pharmacists on the importance of providing each patient with a Medication Guide with each prescription and instructing the patient to read it and assisting the patient to understand the content.
3. 4.a.iii. add
   - In accordance with the United States federal Food, Drug, and Cosmetic ACT (FDCA) 505-1(e) (3), Mallinckrodt will execute a communication plan to HCPs to support implementation of Exalgo REMS for one year following approval of the NDA for Exalgo.
4. Change definition of opioid tolerant to “Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg transdermal fentanyl /hour, 30 mg of oral oxycodone/day, 8 mg of oral hydromorphone/day, 25 mg of oxymorphone /day, or an equianalgesic dose of another opioid, for 1 week or longer. “
5. See attached revised REMS Supporting Document

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.

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

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/s/

JEANNE P PERLA
11/13/2009

MARY E WILLY
11/13/2009
I concur

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** October 28, 2009
Exalgo (hydromorphone HCl) extended-released tablets	21-217	**Comment Set # [1]**
DRISK Scientific Lead: Jeanne Perla		**Reviewers:** DRISK Jeanne Perla PhD., Risk Management Analyst Marcia Britt PhD, Regulatory Health Specialist Mary Willy PhD Deputy Director Review Officer Mathilda Fienkeng, PharmD, Regulatory **DPV** Afrouz Nayernama PharmD, Safety Evaluator
RCM #: 2009-1108		

Materials Reviewed all dated May 22, 2009:
Exalgo proposed REMS
Exalgo supporting document
Educational materials:

- Prescriber Program Brochure
- Prescriber Introductory Letter
- Pharmacy Introductory Letter
- Wholesaler Introductory Letter
- Pain Care Center of Excellence Introductory Letter
- Association Introductory Letter
- Pharmaceutical Compendia Introductory Letter
- DEA Introductory Letter

The comments below are Office of Surveillance and Epidemiology's (OSE's) review of the proposed REMS for Exalgo (hydromorphone HCl).

This review includes revisions of the proposed REMS, Information Letters to the Healthcare Providers, Pharmacist and Professional Associations, and Guide for Healthcare Providers.

Comments to DAARP

The brochure will need to be revised. Should they use the same content guide you have provided other Sponsors in the past?

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:
(1) The risk of overdose caused by exposure to an essentially immediate-release form of hydromorphone due to breaking, chewing, crushing or dissolving Exalgo
(2) 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

A request to remove the following statement is a frequent request from DDMAC. The sponsor added the word (b) (4) Do we leave the statement with the word (b) (4) or leave the statement but remove the word (b) (4)?

The proposed REMS materials present the claim, (b) (4) Eliminate this language.

General comments to Sponsor

1. REMS do not address diversion. Remove all references to diversion. The word misuse can be substituted
2. Patient education can not be included in the communication plan heading of the REMS.
3. There are no elements to assure safe use. Remove all references to the Exalgo Alliance Program
4. 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 (b) (4)
5. REMS materials are not appropriate for use in a promotional manner.
6. The proposed REMS letters will be disseminated at launch. Provide an endpoint (time frame) for disseminating the letters.

A. Goals

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.

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 (b) (4) from the REMS.

C.1 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, (b) (4) 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: (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. (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. The paragraph reads, (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, (b) (4) However, the information regarding the purpose of the program and the REMS risks are presented at the bottom of page one, and on pages two, and three of the letters.

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

C.2 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.

D. 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 90 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.

E. 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

If you 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

If 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:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, 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 90 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

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include 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)
6. Other Relevant Information

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

/s/

JEANNE P PERLA
10/27/2009
Exalgo interim REMS review

MARY E WILLY
10/27/2009
I concur