DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021217 **NDA APPROVAL**

ALZA Corporation
c/o: Premier Research Group
755 Business Center Drive
Horsham, PA 19044

Attention: Susan M. Franks
Director, Regulatory Affairs

Dear Ms. Franks:

Please refer to your new drug application (NDA) dated December 28, 1999, received December 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXALGO (hydromorphone HCl) 8-, 12-, and 16-mg Extended-Release Tablets.

We acknowledge receipt of your submissions dated January 13, February 16, April 28, May 4, November 21, December 5 and 18, 2000, May 12, 2003, May 17 and July 16, 2004, April 14, 2005, October 5, 2007, August 6 and November 6, 2008, and March 10, May 22, June 9 and 23, July 7(2), 8, 13 and 30, August 5, 10, 12, 17 and 25, September 17(2), October 2 (2), 5, 21 (2), 27 (2), and 28, November 17(4) and 25, December 8 (2), 2009, and February 11, 12, 16, 17, 18 and 25, and March 1, 2010.

The May 22, 2009, submission constituted a complete response to our October 27, 2000, action letter.

This new drug application provides for the use of Exalgo (hydromorphone HCl) Extended-Release Tablets for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and Medication Guide. For administrative purposes, please designate this submission, "**SPL for approved NDA 21217**."

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21217**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 2 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 2 years of age who are on around-the-clock opioids and are opioid tolerant is so small that it is impractical to study this population.

We are deferring submission of your pediatric study for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually

according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

1568-1. Deferred pediatric study under PREA, a Phase 1 pharmacokinetic and safety study for the treatment of chronic pain in opioid tolerant pediatric patients ages 7 through 17.

Final Protocol Submission:	October 31, 2010
Study Start Date:	March 31, 2011
Study Completion Date:	March 31, 2012
Final Report Submission:	July 31, 2012

1568-2. Deferred pediatric study under PREA, a Phase 1 pharmacokinetic and safety study for the treatment of chronic pain in opioid tolerant pediatric patients ages 2 to less than 7 years.

Final Protocol Submission:	March 31, 2012
Study Start Date:	September 30, 2012
Study Completion Date:	September 30, 2013
Final Report Submission:	January 30, 2014

Submit final study reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessments

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity that could be associated with the use of Exalgo (hydromorphone HCl).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1568-3. Carcinogenicity study in mice (currently ongoing).

The timetable you submitted on October 20, 2009 states that you are conducting this study according to the following schedule:

Protocol Submitted: October 6, 2005
Study Start: March 24, 2009
Study Completion: May 10, 2011
Final Report Submission: by November 2011

1568-4. Carcinogenicity study in rat (currently ongoing).

The timetable you submitted on October 20, 2009 states that you are conducting this study according to the following schedule:

Protocol Submitted November 21, 2008
Study Start: March 18, 2009
Study Completion: May 3, 2011
Final Report Submission: by November 2011

Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Section 505-1 of the 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)).

Pursuant to 505-1(f)(1), we have determined that Exalgo (hydromorphone HCl) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of abuse, misuse, and overdose, as well as the risk of use of Exalgo (hydromorphone HCl) in non-opioid tolerant individuals. The elements to assure safe, specifically, your plan to ensure that Exalgo (hydromorphone HCl) will only be prescribed by healthcare providers who have particular training under 505-1(f)(3)(A) will mitigate the observed safety risks through achieving REMS goals to inform and train healthcare providers about the potential risks and the safe use of Exalgo (hydromorphone HCl).

Your proposed REMS, submitted on February 25, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for the submission of assessments of the REMS.

As you know, we are considering what REMS elements should be implemented across the class of modified-release opioids to address the risks of: 1) use in non-opioid-tolerant individuals and 2) abuse, misuse, overdose, and addiction. As discussed, once that determination is made, we will notify you in writing and you will be required to submit a modified REMS incorporating those elements.

The REMS assessment plan should include but is not limited to the following:

1. An evaluation of patients' understanding of the serious risks of Exalgo (hydromorphone HCl).

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 (hydromorphone HCl) (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 requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify any submission containing the REMS assessment or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021217 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021217
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021217
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

An expiration dating period of 30 months is granted to the 8 mg Exalgo tablets in the HDPE bottle packaging configuration, stored at 25ºC (77ºF); excursions permitted to 15-30°C (59-86°F).

An expiration dating period of 36 months is granted to the 12 and 16 mg Exalgo tablets in the HDPE bottle packaging configuration, stored at 25ºC (77ºF); excursions permitted to 15-30°C (59-86°F).

Additionally, we remind you of your agreement to perform annual microbial limits testing on stability for the first three post-approval batches for the lowest and highest strengths.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diana L. Walker, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Package Insert
Medication Guide
Carton and Immediate Container Labels
REMS

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/

BOB A RAPPAPORT
03/01/2010