

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-217s000**

**OTHER REVIEW(S)**

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**Date:** March 1, 2010

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia and Rheumatology Products

**Thru:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

**From:** Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff (CSS)

**Subject:** NDA 21-217, Exalgo/Hydromorphone HCl Extended Release, 8 mg, 12 mg, 16 mg, 32 mg tablets. *Sponsor:* Neuromed Pharmaceuticals

This memorandum responds to the Division of Anesthesia, Analgesia and Rheumatology Products's request to CSS to summarize the outcomes of the meeting that took place on January 13, 2010 between members of CSS, the Division and the Deputy Center Director, Dr. Throckmorton. The purpose of the meeting was to discuss managing the risks of abuse and misuse of Exalgo that were identified in the CSS review of 10/23/2009 and further analyzed in CSS communication dated 11/13/2009 that were filed in DARRTS.<sup>1</sup>

The discussion at the meeting focused on the concerns that abuse and misuse of Exalgo may be worse than that of immediate-release hydromorphone, which is already a product that seems to have a disproportionately high ratio of DAWN reports relative to the number of prescriptions, as compared to other opioids. Other instruments, such as data extracted from RADARS also suggest a similar finding for hydromorphone immediate release products. In addition, the safety and abuse risks associated with the 32 mg strength were further discussed.

At the end of the meeting CSS and DAARP agreed to the following:

- 1- DARRP was going to request the Sponsor to delay the marketing of the 32 mg tablets until post-marketing data on the safety associated with the potential abuse and misuse of the lower Exalgo strengths is collected and evaluated. The group concurred that marketing of the 8 mg and 16 mg tablets only could be appropriately carried out with the same REMS that is currently in place for other Schedule II extended release opioids.

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<sup>1</sup> DARRTS, NDA 21-217, CSS Review, Gong, Jianping P, 10/23/09. Gong, Jianping P, 11/13/09.

- 2- DARRP committed to initiating discussions with the Sponsor to initiate similar efforts as those of other sponsors (such as Purdue) that market high potency, high strength extended release opioids, , regarding the following
  - a. Proposing an epidemiological study to gather data to evaluate the impact of the new formulation on the abuse levels of hydromorphone, and
  - b. To work on developing a formulation that is resistant to chewing.

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/

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SILVIA N CALDERON  
03/01/2010

MICHAEL KLEIN  
03/01/2010

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**Date:** November 13, 2009

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia and Rheumatology Products

**Thru:** Michael Klein, Ph.D., Director  
Lori A. Love, M.D., Ph.D., Team Leader  
Controlled Substance Staff (CSS)

**From:** Silvia Calderon, Ph.D., Team Leader  
JianPing Gong, M.D., Ph.D., Medical Officer  
Controlled Substance Staff (CSS)

**Subject:** NDA 21-217, Exalgo/Hydromorphone HCl Extended Release, 8 mg, 12 mg, 16 mg, 32 mg tablets. *Sponsor:* Neuromed Pharmaceuticals

This memorandum responds to the request of the Division of Anesthesia, Analgesia and Rheumatology Products to CSS to discuss management of the risks associated with the abuse and misuse of Exalgo that were identified in the complete CSS review of 10/23/2009 filed in DARRTS.<sup>1</sup> This memorandum summarizes the current knowledge on the abuse potential of hydromorphone and Exalgo, epidemiological data on misuse and abuse of the currently marketed hydromorphone immediate release formulations, and provides an overview of the data presented at the September 23, 2009 joint meeting of the Anesthetic and Life Support Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRMAC).

## CONCLUSIONS

- Exalgo poses high safety risks, associated with misuse, overdose and abuse. This conclusion is based on current knowledge of the pharmacology of hydromorphone, as well as the high dose formulation, lack of tamper resistant characteristics of the formulation, potent reinforcing psychic effects, the recognized history of abuse of hydromorphone, and the proposed extension to a wide range of pain patient populations.
- Current experience demonstrates that the risk management strategies in place to date for OxyContin (that is, a medication guide and educational programs) are not sufficient to mitigate the safety risks associated with the use of Exalgo.

## RECOMMENDATIONS

- If the product is approved, CSS endorses the ALSDAC-DSaRMAC recommendation to accept the Sponsor's proposed REMS program. The Sponsor's program is more stringent than the proposed interim opioid REMS.

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<sup>1</sup> DARRTS, NDA 21-217, CSS Review, Gong, Jianping P, 10/23/09.

- The ALSDAC-DSaRMAC recommended as part of the REMS a phased rollout of the product similar to that approved for Palladone (Hydromorphone extended release capsules, not currently on the market) in 2003. Marketing of Palladone was limited to physicians knowledgeable in the prescribing of potent opioids for management of pain. However, if prescribing of Exalgo is limited to experts in the field of pain management, a low incidence of adverse events associated with inappropriate patient selection, misuse and overdose is expected.
- If a limited introduction phase for the product is considered, we propose a roll out of the product by dosage strength. The introduction on the market of lower strength dosages will allow the Sponsor and the Agency to gain experience on the actual use of the product, while limiting the dose-mediated adverse events that might occur in the context of misuse and abuse.

## BACKGROUND

- Hydromorphone, oxycodone and morphine have a high abuse potential and as such are controlled in C-II of the Controlled Substances Act (CSA). Although these three mu opioid agonists share the same levels of control, the abuse potential of hydromorphone, for the reasons stated below, is greater than that of morphine and oxycodone.
- Hydromorphone offers greater analgesic vs. subjective/psychic effects potencies relative to oxycodone. Hydromorphone is a more potent analgesic than oxycodone, and as such, is not equivalent on a mg per mg basis. At equianalgesic doses, oral hydromorphone is approximately four times more potent than oral oxycodone when physiological opioid effects (miosis, hypotension, analgesia) are compared.<sup>2,3</sup> Thus, a dose of 8-mg hydromorphone (lowest dose proposed for Exalgo) is equivalent in its opioid effects of analgesia, miosis, and respiratory depression to 32 mg of oral oxycodone, and 32 mg of hydromorphone (highest dose proposed for Exalgo) is equivalent in opioid analgesia and physiological effects (miosis and respiratory depression) to approximately 128 mg of oral oxycodone.
- When the subjective effects of liking and euphoria are measured in patients with a prior history of abuse, oral immediate release hydromorphone is somewhat more potent (less than two-fold) than oxycodone.

In the human abuse potential pharmacology study included in the NDA, single dose administration of Exalgo showed a high abuse potential as indicated by the intensity and duration (more than 20 hours) of the positive subjective effects.

- Exalgo tablets use the OROS delivery system. (b) (4)

The proposed label indicates that tablets are to be swallowed whole. However, the Sponsor at the September 23, 2009 joint ALSDAC/ DSaRMAC meeting reported nine cases of misuse by tablet manipulation, including three where medical personnel had split or cut the tablets of the identical product that was marketed abroad between August 2006 and December 2008. Exalgo is marketed by Johnson & Johnson in nine countries under the brand name of Jurnista. In addition, there were two cases where the

<sup>2</sup> Foley, KM. The Treatment of Cancer Pain. *New England J. Med.* 1985, 313 (2), 84-95.

<sup>3</sup> Pereira, J., Lawlor, P., Viganò, A., Dorgan, M., Bruera, E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J. Pain Symptom. Manage* 2001, 22, 672-687.

tablet was chewed. One of these cases resulted in a fatality and the second case resulted in a hospitalization.<sup>4</sup>

- Hydromorphone has a well-documented history of abuse dating back to the 1970's when hydromorphone was the drug of choice among opiate abusers who often administered the drug intravenously after crushing and dissolving the 4-mg immediate release (Dilaudid) tablets. Dilaudid continues to be commonly diverted and abused.

Non-medical emergency department visits in DAWN/per 10,000 prescription ratios for hydromorphone (currently marketed as immediate release products) are higher than the ratios for immediate release oxycodone, and comparable to the ratios for OxyContin (Oxycodone extended release tablets). The ratios of non-medical ED visits per 10,000 prescriptions for hydromorphone immediate release products increased from 34.6 in 2004 to 58.7 in 2007, whereas the ratios for oxycodone immediate release products increased from 7.2 in 2004 to 9.5 in 2007 and for oxycodone extended release products (OxyContin) increased from 42.4 in 2004 to 61.6 in 2007. The calculated ratios for hydromorphone immediate release are comparable to the observed ratios for the extended release oxycodone products.<sup>4</sup> These findings are of a high concern because, if such a high rate of ED visits per 10,000 prescriptions of hydromorphone low dosage strengths (2 mg, 4 mg and 8 mg) is observed, it is predicted that rates of nonmedical ED visits per dispensed prescriptions will increase with the availability of higher strengths of hydromorphone.

- Given the level of current abuse of hydromorphone immediate release tablets (4 mg and 8 mg strengths) relative to oxycodone immediate release tablets and to OxyContin, and the high levels of prescription drug abuse, it is expected that, once on the market, Exalgo tablets (8 mg, 12 mg, 16 mg and 32 mg) will be associated with higher levels of misuse and abuse than OxyContin. Public health consequences of misuse and abuse are a serious safety concern.
- Current data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system has indicated a doubling in the hydromorphone-misuse and abuse-related rates per 1,000 Unique Recipients of Dispensed Drug in a number of different signal detection systems, including those of Drug Diversion, Opioid Treatment Programs, Survey of Key Informants, over the past three quarters. This is very troubling considering that currently the highest dose of hydromorphone available is 8 mg.
- The Sponsor estimated that approximately (b) (4) people in the United States are candidates to use Exalgo, meaning that they are opioid tolerant and with severe to moderate pain.
- The Sponsor recognizes the potential risks of inappropriate patient selection, overdose (intentional and unintentional), misuse and pediatric exposure associated with Exalgo. The Sponsor proposes a Risk Evaluation and Mitigation Strategy (REMS) plan, referred to as the Exalgo Alliance™ Program, which is more stringent than the currently proposed interim opioid REMS that is similar to the one in place for OxyContin. As noted previously, the calculated ratios of DAWN non-medical emergency department visits per 10,000 prescriptions for oxycodone have been increasing for the past four years.
- The members of the joint ALSDAC-DSaRMAC on September 23, 2009<sup>5</sup>, concluded that:

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<sup>4</sup> Transcript:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187490.pdf>

“The committee consensus was that the drug Exalgo is a significantly efficacious drug for a group of opiate tolerant patients. It also has a significant potential for abuse because, like the other opiates, it is very potent, with a high level of subjective liking on the part of addicts. In the spectrum of abuse, it is towards the top of the spectrum of the drugs that are currently in the market. It is reasonable to predict that the abuse of Exalgo will parallel its availability, much like OxyContin.”

“The Committee endorsed the REMS Program as outlined by the sponsor, with the caveat that it should be accomplished in combination with a phased-in introduction of Exalgo into the market. The program should assure that the drug is first prescribed by a particular set of practitioners or provider types, and only in a designated patient population/disease type. A careful phased-in rollout maximizes the potential that this valuable drug enters the market in a way that it allows it to maintain a sustained presence.”

- The members of the ALSDAC-DSaRMAC recommended a phased-in introduction of Exalgo similar to the roll out approved for Palladone (Hydromorphone extended release capsules, not currently on the market). The Palladone Risk Management Program included a phased launch. During this limited introduction phase, sales representatives were supposed to limit the detailing of Palladone for a minimum of 18 months to a subset of physicians that included physicians who regularly manage patients with persistent pain, who prescribe single entity opioids (SEO) and who were identified as high prescribers of SEO.

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<sup>5</sup> Meeting Minutes:  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187630.pdf>

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

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/s/

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Jianping P GONG  
11/13/2009

SILVIA N CALDERON  
11/13/2009

MICHAEL KLEIN on behalf of LORI A LOVE  
11/13/2009

MICHAEL KLEIN  
11/13/2009



**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: November 5, 2009

To: Bob A. Rappaport, Director  
**Division of Analgesia, Anesthesia and Rheumatology  
Products**

Through: **Mary Willy, PhD, Deputy Director**  
**Division of Risk Management (DRISK)**

LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): EXALGO (hydromorphone HCl) Extended Release Tablets  
C-II

Application Type/Number: NDA 21-217

Applicant/sponsor: Neuromed Pharmaceuticals, Inc.

OSE RCM #: 2009-1108

## 1 INTRODUCTION

On May 22, 2009 Neuromed Pharmaceuticals, Inc. submitted a Complete Response to an Approvable Letter issued by FDA on October 27, 2000. The Applicant is seeking approval 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.

This review is written in response to a request by the Division of Analgesia, Anesthesia and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for EXALGO (hydromorphone HCl) Extended Release Tablets. Based on discussion with DAARP, we used the approved Embeda MG dated August 13, 2009 as a comparator for our review. We also reference DRISK's review of the OxyContin MG dated August 2009, because of similar language pertaining to pregnancy and breast-feeding, and withdrawal effects on newborns.

Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DAARP under separate cover.

## 2 MATERIAL REVIEWED

- Draft EXALGO (hydromorphone HCl) Extended Release Tablets Prescribing Information (PI) submitted May 22, 2009 and revised by the Review Division throughout the current review cycle; the most recent version from the Applicant dated October 26, 2009.
- Draft EXALGO (hydromorphone HCl) Extended Release Tablets Medication Guide (MG) submitted on May 22, 2009 and further revised on October 26, 2009.

## 3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- rearranged information due to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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

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/s/

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SHARON R MILLS  
11/05/2009

MARY E WILLY  
11/05/2009  
I concur

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** October 30, 2009

**To:** Diana Walker – Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

**From:** Mathilda Fienkeng – Regulatory Review Officer  
Twyla Thompson – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Through:** Sangeeta Vaswani – Group Leader  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
**NDA 21-217 EXALGO (hydromorphone HCl) Extended Release Tablets CII**

DDMAC has reviewed the proposed product labeling (PI), Medication Guide (Med Guide) and container labeling for EXALGO (hydromorphone HCl) Extended Release Tablets C-II (Exalgo), submitted for consult on June 12, 2009.

The following comments are provided using the updated proposed PI and Med Guide sent via email on October 26, 2009 by Diana Walker. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

**Carton and Container Label**

DDMAC notes that the tradename "EXALGO" is presented with the claim (b) (4) on the container labels. Is this claim part of the approved trade dress? We recommend removing this claim from the graphical presentation of the trade name on all the container labels if it is not part of the trade dress.

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/s/  
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MATHILDA K FIENKENG  
10/31/2009



**MEMORANDUM**  
Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research



**Date:** October 23, 2009

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia and Rheumatology Products

**Through:** Michael Klein, Ph.D., Director  
Lori A. Love, M.D., Ph.D., Lead Medical Officer  
Controlled Substance Staff

**From:** JianPing (John) Gong, M.D., Ph.D., Medical Officer  
Controlled Substance Staff

**Subject:** Consultation on Exalgo (hydromorphone HCl) ER Tablets  
NDA #: 21-217  
Document date: May 22, 2009  
Indication: Moderate to severe pain in opioid tolerant patients  
Strengths: 8, 12, 16, and 32 mg  
Sponsor: Neuromed pharmaceuticals

**Submission:** NDA 21-217 is located in the EDR. CSS reviewed the following documents from the NDA:

- 1) Abuse Liability Assessment: OROS® Hydromorphone Abuse Liability Assessment Report
- 2) Summary of In Vitro Abuse Liability Studies for OROS® Hydromorphone
- 3) Clinical Study Report: NMT 1077-301, A Phase III, variable-dose titration followed by a randomized double-blind study of controlled-release OROS® Hydromorphone compared to placebo in patients with chronic low back pain
- 4) Narratives for patients identified by Neuromed Pharmaceuticals as “Patients of Interest” in Clinical Study NMT 1077-301 because of study medication accountability discrepancies
- 5) Clinical Study Report: C-2004-022-00, A Study to Evaluate the Abuse Potential of OROS® Hydromorphone Compared to Hydromorphone Immediate Release (IR) in Opiate-Experienced Non-dependent Volunteers
- 6) Draft labeling text

**Other Reviewed Materials:**

- 1) Statistical Review and Evaluation, Abuse Potential Study-NDA 21-217, by Ling Chen, Ph.D., Office of Biostatistics, Division of Biometrics, Special Project Team, August 28, 2009

**Background**

The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) consulted the Controlled Substance Staff (CSS) regarding the abuse potential of Exalgo (hydromorphone HCl) Extended Release Tablets for oral administration.

Hydromorphone is a semisynthetic 5-ring morphinan derivative opioid analgesic with effects similar to those of morphine. Interaction with the  $\mu$ -opioid receptor subtype is responsible for most of the clinical effects of hydromorphone.

In the US and some other countries, hydromorphone is currently available as an immediate-release (IR) oral formulation (e.g., Dilaudid, 2, 4, and 8 mg) for treatment of acute and chronic pain, which requires that it be taken continuously every 4 hours.

(b) (4)



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

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/s/

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Jianping P GONG  
10/23/2009

LORI A LOVE  
10/23/2009

MICHAEL KLEIN  
10/23/2009



**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: October 14, 2009

To: Bob Rappaport, MD, Director  
Division of Anesthesia, Analgesia and Rheumatology  
Products

Through: Melina Griffis, RPh, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Exalgo (Hydromorphone Hydrochloride) Extended-  
release Tablet; 8 mg, 12 mg, 16 mg, and 32 mg

Application Type/Number: NDA 021217

Applicant/sponsor: Neuromed Pharmaceuticals, Inc.

OSE RCM #: 2009-1106

## **1 INTRODUCTION**

This review was written in response to a June 8, 2009 request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for an assessment of the labels and labeling in the Applicant's original submission, dated May 22, 2009, to identify areas that could lead to medication errors. The Applicant submitted trade container labels and insert labeling for review and comment.

## **2 MATERIALS REVIEWED**

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis<sup>1</sup> in our evaluation of the labels and labeling submitted as part of the May 22, 2009 submission. (Appendix A).

## **3 RECOMMENDATIONS**

Our evaluation noted areas where information on the label and labeling can be clarified and improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 (*Comments to the Division*) for discussion during the review team's label and labeling meetings. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container labels. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Abolade Adeolu, OSE Regulatory Project manager, at 301-796-4264.

### **3.1 COMMENTS TO THE DIVISION**

#### **A. Insert Labeling**

1. Revise the Dosage and Administration section, subsection 2.1.1, of the labeling to include the maximum starting dose when converting from another opioid, as well as a recommended maximum daily dose after titration.
2. The Dosage and Administration section should highlight the potential for error due to inadvertent substitution which could lead to significant overdose or underdosing of hydromorphone because of the availability of two 8 mg hydromorphone products, Exalgo and Dilaudid. If the clinical review team finds the potential for error to rise to a higher level, the statement could be placed in the precautions section instead of the Dosage and Administration section.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3.2 COMMENTS TO THE APPLICANT

#### A. 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 than 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 (e.g. If the approved REMS allows, delete the statement (b) (4) or relocated to a side panel (e.g. “Each tablet contains...”).
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:
  - a) “ (b) (4)
  - b) (b) (4)
  - c) “ (b) (4)
  - d) Delete the (b) (4) statement as only one statement is required to communicate the usual dose. The statement, (b) (4) ” will ensure that the healthcare practitioner is directed toward more comprehensive dosing information for Exalgo. Additionally the “Once Daily” statement on the principle display panel alerts practitioners of the frequency of administration.
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.

## **APPENDICES**

### **Appendix A**

Container Labels



(b) (4)



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/s/  
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ANNE CRANDALL  
10/14/2009

MELINA N GRIFFIS  
10/14/2009

CAROL A HOLQUIST  
10/14/2009



**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: August 7, 2009

To: Bob Rappaport, M.D, Director  
Division of Anesthesia, Analgesia and Rheumatology Products  
(DAARP)  
Office of New Drugs

Through Lauren Choi, Pharm.D, Team Leader  
Division of Pharmacovigilance II (DPV II)  
Office of Surveillance and Epidemiology

From: Afrouz Nayernama, Pharm.D.  
Safety Evaluator  
Division of Pharmacovigilance II (DPV II)  
Office of Surveillance and Epidemiology

Subject: AERS crude counts of gastrointestinal obstruction and bezoar  
formation associated with the use of oros drug products.

Drug Name(s): Concerta, Covera HS, Ditropan XL, DynaCirc CR, Glucotrol XL,  
Procardia XL, and Sudafed 24

Application Type/Number: N/A

OSE RCM #: 2009-1339

## 1 INTRODUCTION

In preparation for Exalgo (oros hydromorphone) Advisory Committee meeting on September 23, 2009, the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) requested AERS crude counts of gastrointestinal (GI) obstruction and bezoar formation associated with the use of all currently available oros drug products. In addition, DARRP requested that DPVII de-duplicate the AERS reports.

## 2 METHODS AND MATERIAL

### 2.1 DATA SOURCE

The AERS database was searched on August 3, 2009 for domestic and foreign reports of GI obstruction and bezoar formation associated with the use of oros products.

### 2.2 SEARCH CRITERIA

The AERS search criteria are as follows:

- Drug: trade names (Concerta, Covera HS, Ditropan XL, DynaCirc, Glucotrol XL, Procardia XL and Sudafed 24).
- MedDRA Search Terms: Gastrointestinal stenosis and obstruction (HLGT) and Gastrointestinal disorders NEC (HLT).
- Search dates: 1969-8/3/2009

## 3.0 DATA

**Table 1. De-duplicated AERS crude counts of selected GI adverse events associated with the use of oros drug products**

Drug Name	Total number of reports retrieved	Bezoar	<sup>1</sup> GI obstruction	Colonic stenosis	Esophageal stenosis
Concerta	17	-	9	-	-
Covera HS	13	-	11	1	1
Ditropan XL	11	-	4	-	-
DynaCirc	0	0	0	0	0
Glucotrol XL	25	2	2	-	1
Procardia XL	124	21	56	2	7
Sudafed 24	0	0	0	0	0
<b>Total</b>	<b>190</b>	<b>23</b>	<b>82</b>	<b>3</b>	<b>9</b>

### **AERS Limitations:**

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<sup>1</sup> GI obstructions include: intestinal obstruction, small bowel obstruction and GI obstruction (unspecified).

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for particular product or used for comparing risk between products.

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AFROUZ R NAYERNAMA  
09/04/2009

LAUREN Y CHOI  
09/04/2009



**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: August 4, 2009

To: Ellen Fields, MD  
Lead Medical Officer  
Division of Anesthesia, Analgesia, and Rheumatology Products  
Office of Drug Evaluation II

Diana Walker, Ph.D.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products  
Office of Drug Evaluation II

Through: Laura Governale, Pharm.D., MBA  
Drug Use Data Analyst Team Leader  
Division of Epidemiology  
Office of Surveillance and Epidemiology

From: Patty Greene, Pharm.D.  
Drug Use Data Analyst  
Division of Epidemiology  
Office of Surveillance and Epidemiology

Subject: Drug utilization trends for selected immediate-release and extended-release opioid pain products

Drug Name(s): codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone containing products.

Application Type/Number: Various

Applicant/sponsor: Various

OSE RCM #: 2009-1278

\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\*

## 1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) is evaluating Exalgo (oros hydromorphone), NDA 21-217, for an Advisory Committee meeting scheduled September 23, 2009. In support of that evaluation, this review provides utilization data for outpatient dispensed prescriptions by product form, physician specialty group and prescribing indication, for calendar years 2006 through 2008. Drug utilization trends for immediate-release hydromorphone products are compared to selected immediate-release and extended-release opioid products used for pain. Selected opioid products included codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

## 2 METHODS AND MATERIAL

### 2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (*see Appendix 1 for database descriptions*) was used to determine the various retail and non-retail channels of distribution for codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone containing products used for pain.<sup>1</sup> With the exception of codeine containing products, the examination of wholesale sales data by eaches (bottles, packets, etc.) in year 2008 indicates that the majority (55% to 91%) of fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone products were distributed to outpatient pharmacy settings. Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. Codeine containing/acetaminophen products were primarily (62%) distributed to inpatient pharmacy settings. Inpatient pharmacy settings include non-federal hospitals, home health care, clinics, long-term care, federal facilities, prisons, universities, etc. Mail order sales distribution ranged from approximately 1% to 5% of sales for all agents studied. Thus, we examined outpatient utilization patterns. Mail order data are not included in this analysis.

### 2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product form and prescriber specialties using SDI, Vector One®: National (VONA) (*Appendix 1*). Indications for use were obtained from the SDI's Physician's Drug and Diagnosis Audit (PDDA) (*Appendix 1*). From these data sources, estimates of the number of prescriptions dispensed and the number of drug mentions by office-based physicians, were obtained from calendar years 2006 through 2008, inclusive.

## 3 DATA

### 3.1 OUTPATIENT DISPENSED PRESCRIPTIONS BY PRODUCT FORM

Total dispensed prescriptions for selected opioid pain products increased by 12% from approximately 180 million prescriptions in year 2006 to nearly 202 million prescriptions by year 2008. Immediate-release (IR) opioid products accounted for 91% of the selected market with

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<sup>1</sup> IMS Health, IMS Nationals Sales Perspectives™, Year 2008, Data extracted 6-05-09. File: NSPC 2009-970 selected opioids 0906opid.xls and NSPC 2009-970 selected opioids 0906code.xls

over 183 million dispensed prescriptions during year 2008. The top two IR opioid products included hydrocodone and oxycodone containing products with 67% and 21%, respectively, of total dispensed prescriptions for IR formulations. Total dispensed prescriptions for IR hydromorphone increased by 15%-16% each year between 2006 and 2008. By year 2008, approximately 1.9 million prescriptions were dispensed for IR hydromorphone which accounted for 1% of the total IR market. Extended-release (ER) opioid products accounted for approximately 9% (18 million dispensed prescriptions) of the total selected market during year 2008. Oxycodone and fentanyl products accounted for 42% and 30%, respectively, followed by morphine products with 26% of total dispensed prescriptions for ER formulations during year 2008 (*Appendix 2, Table 1*). Palladone (hydromorphone extended-release capsule) was the only marketed ER hydromorphone formulation during the review period and is currently discontinued from the market.

### **3.2 PRESCRIBER SPECIALTIES**

For the entire review period, General Practice/Family Medicine/Doctor of Osteopathy (GP/FM/DO) and Internal Medicine (IM) were the top two prescribing specialties for both immediate-release and extended-release formulations. Dental, Emergency Medicine, and General Surgery were within the top ten prescribing specialties for immediate-release formulations only and combined accounted for approximately 18% of the selected market share in year 2008. Dental providers were the third most common prescribing specialty for IR opioid formulations. For ER opioid formulations, Anesthesiology was the third most common prescribing specialty. The top three prescribing specialties for IR hydromorphone products were GP/FM/DO, IM and Anesthesiology (*Appendix 2, Tables 2 and 3*).

### **3.3 INDICATIONS FOR DRUG USE**

According to office-based physician practices in the U.S., "Surgery follow-up" (V67.0) was the top diagnosis code associated with the use of IR hydromorphone at ~8% for calendar years 2006 to 2008. The second most common use for IR hydromorphone was "Abdominal Pain" (ICD-9 789.0) at ~6% for the same period (*Table 4*).

## **4 DISCUSSION**

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone products are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

## **5 CONCLUSIONS**

For the entire review period, immediate-release formulations accounted for nearly 91% of the selected market for opioid pain products. Immediate-release hydromorphone accounted for approximately 1% of dispensed prescription for the selected market by year 2008. General Practice/Family Medicine/Doctor of Osteopathy, Internal Medicine and Anesthesiology were the top three prescribing specialties for immediate-release hydromorphone. The top diagnosis code associated with the use of immediate-release hydromorphone was “Surgery follow-up” (ICD-9 V67.0).

## **APPENDIX 1: DATABASE DESCRIPTIONS**

### ***SDI Vector One®: National (VONA)***

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

### ***SDI Physician Drug & Diagnosis Audit (PDDA)***

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

### ***IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail***

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

APPENDIX 2: TABLES

**Table 1. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for selected opioid pain agents by product form, January 1, 2006 - December 31, 2008**

	2006		2007		2008	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	179,690,966	100.0%	192,502,779	100.0%	201,757,684	100.0%
<b>Immediate Release</b>	164,246,443	91.4%	175,377,090	91.1%	183,332,224	90.9%
hydrocodone	111,750,006	68.0%	118,944,252	67.8%	122,736,942	66.9%
oxycodone	30,668,659	18.7%	34,668,180	19.8%	38,895,131	21.2%
codeine	14,966,588	9.1%	14,254,899	8.1%	13,554,150	7.4%
methadone	3,913,044	2.4%	4,181,652	2.4%	4,439,950	2.4%
hydromorphone	1,388,900	0.8%	1,617,911	0.9%	1,868,423	1.0%
morphine	1,191,911	0.7%	1,303,570	0.7%	1,427,835	0.8%
fentanyl	359,106	0.2%	344,667	0.2%	300,840	0.2%
oxymorphone	8,229	0.0%	61,959	0.0%	108,953	0.1%
<b>Extended Release</b>	15,444,523	8.6%	17,125,689	8.9%	18,425,460	9.1%
oxycodone	6,960,034	45.1%	7,541,029	44.0%	7,816,692	42.4%
fentanyl	4,734,610	30.7%	5,195,507	30.3%	5,378,501	29.2%
morphine	3,729,690	24.1%	4,194,878	24.5%	4,830,702	26.2%
oxymorphone	20,172	0.1%	194,274	1.1%	399,565	2.2%
hydromorphone	17	0.0%	1	0.0%	--	--

Source: SDI Vector One®: National, Data Extracted 8-2009. File: VONA 2009-970 selected opioids form 08-18-09.xls

**Table 2. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for selected\* opioid pain agents by product form and top 10 prescribing specialties, January 1, 2006 - December 31, 2008**

	2006		2007		2008	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	<b>179,658,813</b>	<b>100.0%</b>	<b>192,314,065</b>	<b>100.0%</b>	<b>201,569,753</b>	<b>100.0%</b>
<b>Immediate Release</b>	<b>164,214,355</b>	<b>91.4%</b>	<b>175,188,401</b>	<b>91.1%</b>	<b>183,144,243</b>	<b>90.9%</b>
GP/FM/DO	38,491,008	23.4%	41,805,985	23.9%	44,116,271	24.1%
INTERNAL MEDICINE	22,335,512	13.6%	24,149,915	13.8%	25,539,094	13.9%
DENTAL	17,597,927	10.7%	17,984,701	10.3%	17,483,399	9.5%
ORTH SURG	13,955,969	8.5%	14,374,825	8.2%	14,350,030	7.8%
EMERGENCY MEDICINE	9,562,843	5.8%	9,975,715	5.7%	10,020,693	5.5%
UNSPEC	7,742,673	4.7%	7,870,936	4.5%	9,605,934	5.2%
ANESTHESIOLOGY	5,843,061	3.6%	6,547,843	3.7%	6,864,451	3.7%
PHYSICIAN ASSISTANT	4,473,112	2.7%	5,629,385	3.2%	6,726,089	3.7%
NURSE PRACTITIONER	3,719,753	2.3%	4,698,482	2.7%	5,651,746	3.1%
GENERAL SURGERY	4,862,019	3.0%	4,994,622	2.9%	4,948,581	2.7%
All Others	35,630,478	21.7%	37,155,992	21.2%	37,837,955	20.7%
<b>Extended Release</b>	<b>15,444,458</b>	<b>8.6%</b>	<b>17,125,664</b>	<b>8.9%</b>	<b>18,425,510</b>	<b>9.1%</b>
GP/FM/DO	4,266,027	27.6%	4,682,843	27.3%	4,967,068	27.0%
INTERNAL MEDICINE	2,837,932	18.4%	3,083,146	18.0%	3,211,327	17.4%
ANESTHESIOLOGY	2,072,462	13.4%	2,368,817	13.8%	2,461,774	13.4%
PHYSICAL MEDICINE & REHAB	1,141,877	7.4%	1,309,292	7.6%	1,596,453	8.7%
UNSPEC	657,909	4.3%	743,316	4.3%	956,137	5.2%
NURSE PRACTITIONER	622,925	4.0%	771,395	4.5%	948,687	5.1%
PHYSICIAN ASSISTANT	406,457	2.6%	520,713	3.0%	675,522	3.7%
NEUROLOGY	437,650	2.8%	478,060	2.8%	524,164	2.8%
ORTH SURG	395,807	2.6%	418,205	2.4%	410,891	2.2%
HEMATOLOGY	327,682	2.1%	346,448	2.0%	363,586	2.0%
All Others	2,277,730	14.7%	2,403,429	14.0%	2,309,901	12.5%

Source: SDI Vector One®: National, Data Extracted 6-2009 File: VONA 2009-970 selected opioids form MD 06-05-09 xls

\*Selected opioids: oxycodone, hydrocodone, morphine, methadone, hydromorphone, fentanyl, oxymorphone, and codeine

**Table 3. Total number of dispensed prescriptions for hydromorphone in outpatient retail pharmacies by top 10 prescribing specialties, years 2006 - 2008**

	JAN 2006 - DEC 2008	
	Retail TRxs N	Share %
<b>hydromorphone</b>	<b>4,935,659</b>	<b>100.0%</b>
<b>GP/FM/DO</b>	861,279	17.5%
<b>INTERNAL MEDICINE</b>	757,399	15.3%
<b>ANESTHESIOLOGY</b>	523,792	10.6%
<b>EMERGENCY MEDICINE</b>	291,976	5.9%
<b>UNSPEC</b>	256,866	5.2%
<b>ORTH SURG</b>	244,788	5.0%
<b>PHYSICAL MEDICINE &amp; REHAB</b>	221,864	4.5%
<b>PHYSICIAN ASSISTANT</b>	186,918	3.8%
<b>NURSE PRACTITIONER</b>	175,888	3.6%
<b>ONCOLOGY</b>	172,662	3.5%
<b>All Others</b>	1,242,227	25.2%

Source: SDI Vector One®: National, Data Extracted Aug-2009. File: VONA 2009-1278 Hydromorphone MD 08-03-09.xls

\*GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

**Table 4. Top 10 diagnoses associated with the use\* of hydromorphone as reported by office-based physician practices, years 2006 - 2008**

	JAN 2006 - DEC 2008	
	Uses (000)	Share %
<b>hydromorphone</b>	<b>2,042</b>	<b>100.0%</b>
V670 SURGERY FOLLOW-UP	160	7.8%
7890 ABDOMINAL PAIN	122	6.0%
7245 BACKACHE NOS	90	4.4%
7295 PAIN IN LIMB	54	2.6%
7194 PAIN IN JOINT	52	2.6%
1629 MAL NEO BRONCH/LUNG NOS	49	2.4%
8404 SPRAIN ROTATOR CUFF	44	2.2%
5920 CALCULUS OF KIDNEY	42	2.0%
1991 MALIGNANT NEOPLASM NOS	41	2.0%
1749 MALIGN NEOPL BREAST NOS	38	1.9%
All Others	1,350	66.1%

Source: SDI Physician Drug and Diagnosis Audit, Extracted Aug-2009. File: PDDA 2009-1278 Hydromorphone 08-12-09.xls

\* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

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PATTY A GREENE

08/21/2009

LAURA A GOVERNALE

08/21/2009

Cleared for AC background package

## SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 21-217
APPLICANT	Neuromed Pharmaceuticals
DRUG NAME	EXALGO (hydromorphone hydrochloride)
SUBMISSION DATE	May 22, 2009
SEALD REVIEW DATE	November 2, 2009
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

33 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

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DEBRA C BEITZELL  
11/02/2009  
SEALD comments sent to DAARP on 11/2/09.

LAURIE B BURKE  
11/03/2009

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

---

**Date:** November 30, 2005

**To:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia, and Rheumatology (HFD-170)

**Through:** Deborah Leiderman, M.D., Director  
Michael Klein, Ph.D., Team Leader  
Silvia Calderon, Ph.D., Team Leader

**From:** Geoffrey Zeldes, M.D., Pharm.D., Medical Officer  
Controlled Substance Staff (HFD-009)

**Subject:** Review of NDA 21-217, OROS hydromorphone (8, 16, 32, 64 mg tab)  
**Indication:** long term management of moderate to severe pain  
**Date of Submission:** September 29, 2005  
**Sponsor:** ALZA Corporation

**Background**

OROS hydromorphone is a controlled-release formulation of hydromorphone based on ALZA's osmotic OROS technology designed to be a once-daily oral formulation to benefit patients with chronic pain conditions.

An approvable letter was issued by the FDA on 27 October 2000 for NDA 21,217 with a clinical comment noting a major clinical deficiency. The sponsor was asked to "conduct an adequate and well-controlled study, with multiple dosing of the to-be-marketed formulation, in the setting of moderate to severe pain, to establish the efficacy of the product".

The current background package was prepared by the sponsor to support a new clinical efficacy study. Results and analysis of a "pivotal" efficacy study are presented. Sections are also included discussing "Potential for Abuse" and "Summary of Benefits and Risks with OROS Hydromorphone", which includes sections on "Efficacy and Abuse Potential". Although there were no specific abuse liability questions from the sponsor, CSS was asked to review this new information. Portions of this consult are reproduced from the document.

**Discussion**

Use of this product does not achieve adequate plasma levels of hydromorphone. The issues of abuse potential and safety will become important when the product is shown to deliver adequate plasma levels of hydromorphone.

Results of new sponsor studies which were designed to prove efficacy failed to do so. The “pivotal” study presented by the sponsor does not show statistically significant efficacy. This product does not release enough drug to achieve therapeutic plasma levels. The findings of this study with regard to the PK profile of the higher doses of the new OROS formulation bring into question the design and properties of the dosage form and should impact the design of future clinical trials aimed to prove efficacy.

**Conclusions**

1. Drug liking scores correlated directly with plasma hydromorphone plateau levels, hence the low scores in this study provides evidence that this product is not achieving high enough drug plasma levels.
2. No conclusion can be reached about the abuse liability or “liking” findings given the failure of the product to achieve adequate plasma levels.
3. Hydromorphone OROS formulation is readily disrupted mechanically.

**Recommendations**

Study C-2004-022 is the first direct comparison of the pharmacokinetics of the OROS hydromorphone system vs. the IR dosage form. The complete PK/PD data set from this study is not yet available. The summary data provided by the sponsor indicate low bioavailability from this product. The completed study data, when available, must be carefully reviewed.

A full report and summary data from Study C-2004-022 should be submitted as part of the NDA resubmission.

CSS will review future abuse liability data submissions. Any change from the present formulation will require a new abuse liability evaluation.

## **ADDENDUM**

### **Submission Review**

Abuse Liability Study C-2004-022 was designed to evaluate the abuse potential of single doses of OROS hydromorphone (comparing both intact and crushed tablets), hydromorphone immediate-release (IR), and placebo. The study also evaluated the PK/PD relationship of the OROS and IR hydromorphone formulations on measures of abuse potential.

Subjects in one treatment group were administered orally crushed encapsulated OROS tablets. The PK profile of crushed OROS hydromorphone 8 mg was similar to that of hydromorphone 8 mg IR. This shows that the advantages of the OROS dosage form can be defeated by simply crushing the tablet and ingesting the powder. This raises safety and abuse liability issues for the higher strength OROS tablets, which can contain up to 64 mg of hydromorphone. Dose-normalized  $C_{max}$  values for the 3 intact OROS treatments (16 mg, 32 mg, and 64 mg) were lower than the  $C_{max}$  for hydromorphone 8 mg IR.  $C_{max}$  and  $AUC_t$  values for OROS hydromorphone 16 mg, 32 mg, and 64 mg were dose proportional. In general, for all treatments the PD results paralleled the PK profiles, i.e., lower maximum PD scores after OROS hydromorphone treatments than after hydromorphone IR.

The C-2004-022 study also showed that there was no statistical difference between OROS 32 mg or 64 mg and 8 mg IR for the primary endpoint of overall drug liking. In addition, doses 4- to 8-fold higher were needed with the OROS formulation to achieve the same maximum response seen with the 8 mg formulation. It was also shown that there is a delayed maximum response (8 to 16 hours after dosing) with the OROS formulation. The sponsor concludes that these findings are advantages of the OROS drug delivery system.

The sponsor claims that based on the abuse liability study (C-2004-022) that the OROS dosing form appears to have a decreased abuse liability, but also notes that the OROS product has diminished bioavailability based on PK/PD studies when compared to the 8 mg IR formulation. Lower overall “drug liking” effect observed after the administration of OROS 32 mg or 64 mg tablets, when compared with the effect of 8 mg IR tablets, is most likely correlated with the similar low plasma levels achieved. The findings of the abuse liability study are more likely based on this PK data than this dosage form is intrinsically safer than the IR form.

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Geoffrey Zeldes  
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Silvia Calderon  
11/30/2005 10:25:46 AM  
CHEMIST

Deborah Leiderman  
12/1/2005 12:25:48 PM  
MEDICAL OFFICER



(b) (4)

1. All study retention samples were not kept at (b) (4) (b) (4). They were returned to the sponsor upon their request.

The sponsor, Knoll Pharmaceutical Company (Knoll), failed to comply with CFR 320.38 in that the study test articles (i.e., test and reference hydromorphone ER formulations, and naltrexone HCl tablets) used in the bioequivalence study were not retained at (b) (4). Consequently, the study test articles could not be collected, and verified by the FDA laboratory.

An audit of the study drug shipment invoice and correspondence file at (b) (4) revealed that the lot numbers of the study test articles were not identified on the shipment invoice or on the label of each drug bottle. Knoll provided the lot numbers to (b) (4) only upon a requested by (b) (4) at a later date. This finding raised questions on identify of the study test articles.

2. Many SAS subroutines used in the pharmacokinetic and statistical data analyses were developed in-house. There is no documentation to show that these SAS subroutines were validated.

(b) (4) acknowledged this finding and is currently validating these SAS subroutines. The results of the validation will be submitted to the Agency for review.

3. The freezer temperature chart for freezer 101, over the study period, indicated that the temperature of this freezer was at or greater than 0°C for more than one hour on three different occasions. There is no documentation on file to provide explanation or action taken in response to these events.

(b) (4) explained that the temperature of freezer #101 was monitored once-a-day using a thermometer placed in this freezer. In addition, the freezer temperature was monitored continuously using a portable continuous temperature-monitoring device. (b) (4) speculated that the portable temperature-monitoring device might have been taken out of the freezer during the above cited occasions. This explanation is not acceptable, as it is not support by any documentation. However, because the bench top stability for hydromorphone at ambient temperature is > 6 hours, this

observation should not affect the integrity of the hydromorphone study samples.

(b) (4)

4. The accuracy and precision of the hydromorphone assay were not accurately reported as QC's with significant deviation from the nominal values were considered as an outlier and were excluded from summary statistic tables.
5. The first seven hydromorphone validation runs failed to meet the acceptable criteria and were rejected. These failed runs were not mentioned in the final validation report.

Items 4 and 5 are related to the objectionable reporting practice at (b) (4). These items should not impact on the outcomes of the hydromorphone study.

Conclusion:

The Division of Scientific Investigations recommends that Study DO-129 be not accepted for review. Knoll has failed to retain study test articles at (b) (4). Consequently, the study retention samples could not be collected and verified by the FDA laboratory as required by CFR 320.38 (see 483 Item 1). Following your review, please attach this transmittal memo to the original NDA submission.

*Martin K. Yau 7/25/00*  
Martin K. Yau, Ph.D.

DSI Final Classification:

VAI -  
VAI -

(b) (4)

CC:

HFD-340 Lepad  
HFD-345 Viswanathan/Yau  
HFD-341 CF/RF  
HFD-170 Milstein  
HFD-870 SM Huang/Uppoor/TM Chen  
HFR-SW1540 Martinez  
HFR-SW350 Montgomery  
HFR-SW3515 Nelson  
Draft: MKY 7/21/00  
DSI:5330;0:\BE\EIRCOVER\21217knoll.Dil.doc

NDA 21-217 / Archival  
NDA 21-217 / Div

## SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 21-217
APPLICANT	Neuromed Pharmaceuticals
DRUG NAME	EXALGO (hydromorphone hydrochloride)
SUBMISSION DATE	May 22, 2009
SEALD REVIEW DATE	November 2, 2009
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

33 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

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

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DEBRA C BEITZELL  
11/02/2009  
SEALD comments sent to DAARP on 11/2/09.

LAURIE B BURKE  
11/03/2009

**MEMORANDUM**

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

PID#: D000174

DATE: JUN - 2 2000

FROM: Denise P. Toyer, Pharm.D.  
Safety Evaluator

Division of Drug Risk Evaluation II, HFD-440

THROUGH: Evelyn Rodriguez, M.D., M.P.H., Director  
Division of Drug Risk Evaluation II, HFD-440

TO: Cynthia McCormick, M.D., Director  
Division of Critical Care and Anesthetic Drug Products, HFD-170

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW

Consult: Drug(s): Drugs using the OROS Delivery System  
Ditropan XL, DynaCirc CR, Efidac 24, Glucotrol XL,  
Minipress XL, Procardia XL, Sudafed 24, and Volmax

Reaction: Intestinal Obstruction

**EXECUTIVE SUMMARY**

A consult was received from the Division of Critical Care and Anesthetic Drug Products (DCCADP) requesting a review of the Adverse Event Reporting System for cases of intestinal obstruction associated with the use of Covera HS, Ditropan XL, DynaCirc CR, Efidac 24, Glucotrol XL, Minipress XL, Procardia XL, Sudafed 24, or Volmax. The Division is currently reviewing a new drug application (NDA) for Dilaudid CR, a controlled release formulation that uses an OROS delivery system. A search of the Adverse Event Reporting System identified 50 unduplicated cases of gastrointestinal obstruction and/or bezoars with the following distribution: Procardia XL (44), Covera-HS (3), Ditropan XL (1), and Glucotrol XL (1), and Efidac 24 (1). Gastrointestinal obstruction and/or bezoars developed in patients with and without a pre-existing history of gastrointestinal disorders including constipation. Patients complained of nausea, vomiting, abdominal pain, or weight loss prior to the diagnosis of the obstruction. Some patients vomited substantial quantities of Procardia XL tablets after the symptoms occurred. The labeling for Dilaudid CR should address the risk of gastrointestinal obstruction in patients with and without pre-existing gastrointestinal problems including chronic constipation.

## **BACKGROUND**

A consult was received from the Division of Critical Care and Anesthetic Drug Products (DCCADP) to review the Adverse Event Reporting System (AERS) for cases of intestinal obstruction associated with the use of Covera HS, DynaCirc CR, Efidac 24, Glucotrol XL, Minipress XL, Procardia XL, Sudafed 24, and Volmax. These drugs utilize an OROS delivery system. [Glucotrol XL, Minipress XL, Sudafed 24, and Procardia XL utilize an OROS delivery system but the labeling lists the system as the Gastrointestinal Therapeutic System (GITS).] The Division is currently reviewing a new drug application for Dilaudid CR that uses an OROS delivery system.

The OROS delivery system provides rate-controlled delivery of the drug, in addition to reducing dosing intervals. The delivery rate of the medication is independent of the gastrointestinal acidity, alkalinity, or food content. The system involves a push-pull tablet that has a semi-permeable rate-controlling membrane surrounding an osmotic core. The osmotic core contains a push layer and a drug layer. Once the tablet enters the gastrointestinal tract, water enters the tablet, through the semi-permeable membrane, and allows the push layer to enlarge, thereby releasing the drug through laser-drilled holes at a controlled rate. The “empty shell” is then eliminated from the body through the gastrointestinal tract. Patients may notice a “ghost shell” or empty pill in their stool.<sup>1</sup>

## **LABELING**

The labeling for the listed products contains varying degrees of information pertaining to the possible occurrence of intestinal obstruction. Minipress XL is not currently marketed in the United States and therefore labeling is unavailable.

### **Covera HS, Ditropan XL, DynaCirc CR, Procardia XL, and Volmax**

These products all contain a general statement in the PRECAUTIONS section of the labeling that indicates that the products should be used with caution in patients with pre-existing gastrointestinal narrowing of any origin. The labeling also notes that reports (i.e., rare) of obstructive symptoms have occurred in other products using similar delivery systems. The INFORMATION FOR PATIENTS section of the Volmax and DynaCirc CR labeling contains a statement that the outer shell is not absorbed and may be occasionally seen in the patients' stool.

The labeling for Ditropan XL also notes that the product is contraindicated in patients with gastric retention or patients who are at risk for developing this condition. However, the labeling for Covera HS indicates that data are not available for patients with extremely short GI transit times.

Glucotrol XL, Sudafed 24, and Efidac 24 (both Chlorpheniramine and Pseudoephedrine)

These products contain a statement similar to the general statement listed above in the WARNINGS section of their labeling. Sudafed 24 and Efidac 24 labeling, both over-the-counter (OTC) products, indicates that patients may notice the product in their stool.

**LITERATURE**

As of May 12, 2000, a MEDLINE search of the published English-language literature, using the terms: gastrointestinal obstruction, bezoar, and the names of the aforementioned products, produced fourteen citations. These citations included a letter to the editor on Procardia XL bezoars and four case reports on gastrointestinal obstruction pertaining to Procardia XL. One of these cases involved a 79-year old male with a history of colon cancer (approximately 20 years ago with a recent recurrence) and hypothyroidism. Approximately 1.5 years after a sigmoid colectomy for the colon cancer recurrence, the patient was evaluated for a rectosigmoid anastomotic stricture. Barium enema revealed pill-shaped densities throughout the distal ileum and the remaining left colon (see figure 1). The patient's only complaints were mild crampy lower abdominal pain and anorexia. Approximately 6 months later the patient complained of a ten pound weight loss. The Procardia XL was discontinued and the patient underwent a sigmoidoscopy to dilate the stricture. Three months later the patient was diagnosed with a mid-ileal obstruction from adhesions that required resection of his infarcted bowel. However, during the surgery, no Procardia XL shells were found and his stricture had improved. The patient recovered.<sup>2</sup>

The consensus in the reported cases is that this dosage form should be used with caution in patients with pathologic or iatrogenic narrowing of the gastrointestinal tract. Additionally, patients with reduced gastrointestinal tract motility caused by age, diabetes mellitus, hypothyroidism, or medications should be carefully monitored for any symptoms related to gastrointestinal obstruction. Finally, patients using this dosage form who present with nausea, vomiting, early satiety, and weight loss should be evaluated for the possibility of obstruction and/or the formation of pharmacological bezoars.<sup>2,3,4</sup>

**Figure One**

**Barium enema revealing many pill-shaped densities throughout distal ileum and the remaining left colon with dilation of the sigmoid colon.**



## **SELECTION OF CASES**

The Adverse Event Reporting System (AERS) was searched using the preferred terms (PT) “intestinal obstruction” and “bezoar.” Fifty unduplicated cases were identified with the following distribution: Procardia XL (44), Covera-HS (3), Ditropan XL (1), and Glucotrol XL (1), and Efidac 24 (1). The Ditropan XL and representative Procardia XL cases will be presented.

### **Ditropan XL**

#### **ISR# 3302707-6-00-01 (MFG. #4707), Domestic**

A 74-year old female with a history of hypertension, uterine cancer, ventral hernia repair, and occasional constipation presented to the emergency room with complaints of nausea, vomiting, and abdominal pain after increasing her Ditropan XL from 5 mg to 10 mg daily. She was diagnosed with significant stool retention without bowel obstruction and a urinary tract infection. She was discharged on magnesium citrate and Bactrim and told to discontinue the Ditropan XL. Twenty-four hours later the patient was admitted to the hospital with worsening abdominal pain. A x-ray revealed an early bowel obstruction. The patient was treated with enemas and intravenous fluids and was discharged four days later.

### **Procardia XL**

#### ***Demographics***

<b>Age (n = 37)</b>	Range 40 to 86 years (Mean = 62 and Median = 62)
<b>Gender</b>	Female = 25; Male = 21
<b>Date of Event (n = 41)</b>	1990 = 5; 1991 = 2; 1992 = 8; 1993 = 6; 1994 = 7; 1995 = 8; 1996 = 4; 1997 = 1; 1998 = 0; 1999 = 0
<b>Report Location</b>	Domestic = 43; Unknown = 1
<b>Tablets Discovered (n = 38)</b>	Range 1 to 500
<b>Hx of GI problems*</b>	18 cases

[\* Crohn’s disease, pyloric stenosis, ischemic bowel, colectomy (due to small bowel obstruction/colon cancer), ulcerative colitis, intestinal adhesions, strictures, and diverticulitis]

#### **ISR# 1563580-X (MFG. # 9307258), Domestic**

A pharmacist reports that a 63-year old female patient with an unknown medical history was taking Procardia XL 60 mg for 2 months when she started to complain of an inability to “keep food down.” She was admitted to the hospital where “many” XL shells were removed from her intestines.

PID # D000174

ISR# 1677367-0 (Direct), Domestic

A 74-year old bedridden, female with a history of bleeding ulcers, stroke, and chronic use of laxatives for constipation died from respiratory collapse with contributing cardiac arrhythmia and partial large bowel obstruction. The patient's physician indicated that her lumen was open but her bowel "did not work well." The report notes that the patient had "spent casings or shells" in her colon which would have required several days for normal removal.

ISR# 1471656-0 (Direct), Domestic

A 68-year old female with a history of coronary heart disease (s/p angioplasty), diabetes, hypertension, peripheral vascular disease, hypothyroidism, esophagitis, and cholelithiasis underwent an upper endoscopy following an abnormal upper GI. The upper GI indicated that the patient had a gastric mass. The upper endoscopy revealed "hundreds" of Procardia XL tablets "tightly bound together." The patient was not completely obstructed. She underwent gastric surgery to remove the bezoar from her stomach.

CASE# 5167515 (Direct), Domestic

A 78-year old female was admitted to the hospital after complaints of recurrent left lower quadrant abdominal pain, tenderness, cramping, abdominal pain, and weight loss. She had a past history of diverticular disease with a sigmoid colon resection. Severe diverticular disease of the colon and a possible mass were revealed by a barium enema and verified by CT scan. During laparotomy a "ball of pills" was discovered in the small bowel. A small bowel resection was conducted.

ISR# 895041-5 (MFG.#L-1b892), Domestic

A 69-year old female developed a sudden onset of right abdominal pain. The patient was admitted to the hospital after CT scan indicated an infiltrating lesion of cecum. The patient was treated with broad-spectrum antibiotics and diet modification. The patient's symptoms improved. A right colon resection was completed and no mass was found. A large ulcerated area was found in the ascending colon. Procardia XL tablets were found in the ulcerated area. The patient had a history of coronary artery disease, hypertension and coronary artery disease. Her medication regimen included Mevacor, Nitroglycerin, Ecotrin, and "Vascon."

ISR# 1845379-X (MFG.#961194), Domestic

ISR# 1396976-X (MFG.#9304314), Domestic

ISR# 1402714-4 (MFG.#9303429), Domestic

The following three cases involve patients who all took Procardia XL and later vomited tablets. A 68-year old man complained of epigastric distress and nausea. He subsequently vomited 19 tablets. A 72-year old man vomited eleven tablets on one day and 3 tablets the following day. Finally, a 61-year old woman with a history of

“colovesical fistule,” COPD, and nervousness experienced stomach cramps and vomiting. The vomitus contained 12 tablets. The Procardia XL was discontinued and the cramps and vomiting resolved. Six months later the patient vomited 30 Procardia XL tablets.

## **DISCUSSION**

Procardia XL was the only product with a substantial number of cases of gastrointestinal obstruction in the AERS database. Additionally, only the Procardia XL cases noted that bezoars (i.e., used shells or ghost tablets) were found within the gastrointestinal tract. The other cases noted the obstruction but did not find any tablets within the gastrointestinal tract. Procardia XL was approved prior to the other products (i.e., 1989 versus 1992-1996) and was the first sustained release nifedipine formulation marketed. These factors may contribute to the high number of cases for Procardia XL. In 1992 and 1995, eight cases of GI obstruction/bezoars were identified each year for Procardia XL. The number of cases remained constant from 1992 through 1995 and has consistently decreased since that time.

Nineteen (38%) of the fifty cases involved patients who had a pre-existing gastrointestinal problem which may have contributed to the adverse event. Patients had the following gastrointestinal pre-existing conditions: Crohns disease and ulcerative colitis with resection; diverticulitis; intestinal adhesions and strictures; pyloric stenosis, ischemic bowel and colectomy. Gastrointestinal narrowing and retention disorders are the only pre-existing conditions listed in the labeling as a contraindication or warning for these products.

The labeling for Dilaudid Tablets notes that: “Prolonged administration of Dilaudid may produce constipation.” In two of the cases listed above the patients had a history of occasional and chronic constipation. Chronic constipation may be a contributing factor to bowel obstruction.

## **OPDRA CONCLUSION**

The OROS delivery system may be a contributing factor to the development of gastrointestinal obstruction. The development of constipation as an adverse event of hydromorphone therapy may also be a contributing factor. The labeling for Dilaudid CR should address the risk of gastrointestinal obstruction in patients with and without pre-existing gastrointestinal problems including constipation.



**Denise P. Toyer, Pharm.D.**  
**Safety Evaluator**

**Concur:**



**Toni Piazza-Hepp, Pharm.D.**  
**Team Leader**

**References:**

1. [www.ditropanxl.com/pros/oros.htm](http://www.ditropanxl.com/pros/oros.htm)
2. Georgopoulos S, Gerdes H. Retention of Nifedipine Extended Release Tabs in a Patient with a Colonic Stricture. *American Journal of Gastroenterology*. December 1995; 90(12): 2224-2226.
3. Stack PE, Patel NR, et al. Pharmacobezoars—The Irony of the Antidote: First Case Report of Nifedipine XL Bezoar. *Journal of Clinical Gastroenterology*. October 1994; 19(3): 264-265.
4. Reid T, Rubins JB, et al. Colonic Medication Bezoar From Extended-Release Nifedipine and Procainamide. *Archives of Family Medicine*. August 1995; 4(8): 715-717.

PID # D000174

Orig. NDA 21-217

Orig. IND (b) (4)

Orig. NDA 20-897

HFD-170/DIVISION FILE

HFD-170/PM/MO/MO-TL/McCormick

HFD-440/Rodriguez/Piazza-Hepp/Toyer/Chron/Drug

HFD-400/Honig

HFD-110/PM/MO/N19684, 20336, 19775

HFD-570/PM/MO/N19604

HFD-510/PM/MO/N20329

HFD-560/PM/MO/N19672, 20021, 19746