FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

M E M O R A N D U M

DATE: August 25, 2009

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the September 23, 2009 ALSDAC Meeting to Discuss NDA 21-217 for Exalgo, an Extended-Release Formulation of Hydromorphone

At this joint meeting of the ALSDAC and DSaRM, we will be discussing an application submitted to the Agency by Neuromed, Inc. for an extended-release formulation of hydromorphone known as Exalgo. Exalgo is a once-daily formulation of hydromorphone intended for the treatment of moderate to severe pain in patients requiring an opioid analgesic over an extended period of time. Currently, the only hydromorphone available as an oral formulation in the United States is immediate-release hydromorphone indicated for the management of acute and chronic pain and dosed every 4 to 6 hours.

Palladone, an extended-release formulation of hydromorphone, was approved in September, 2004. A meeting of the ALSDAC was held in September, 2003, at which the abuse liability and options for the risk management of Palladone were discussed in detail. Based on the data presented at that meeting documenting that hydromorphone is a highly sought after drug of abuse, and due to the fact that the dosages of the Palladone formulation were quite high, the committee members recommended a phased marketing rollout, starting with the lowest dosage strengths, targeting specific specialties and prescribers, and incorporating monitoring of overdose or misuse in decisions on whether to expand marketing from one phase to the next. Palladone was subsequently removed from the market in July, 2005, due to findings of extensive dose-dumping in the presence of alcohol.

During this meeting you will hear presentations on the efficacy and safety of Exalgo, the extent of the underlying problems of misuse and abuse of opioid analgesics, drug utilization trends for hydromorphone, data regarding the abuse liability of hydromorphone, in general, and Exalgo, in particular, and options for the management of the risks associated with this product, including the proposed risk management plan previously put in place for Palladone. You will be asked to discuss where Exalgo lies in the spectrum of abusability compared to other opioid drug products and, based on that, where it best fits into the spectrum of risk management options.

I am grateful for your participation and thank you in advance for your assistance in providing your expertise and your insights to us as we move forward with decisions regarding the implementation of a risk management strategy that will, hopefully, mitigate the risks of abuse, overdose and addiction that are likely to occur with the introduction of Exalgo into the analgesic armamentarium.

Hydromorphone Extended Release (HMER) Regulatory History

Palladone History – Key Milestones

- December 28, 1998 – Purdue Pharma submitted NDA for Palladone™ (Hydromorphone hydrochloride extended-release capsules in dosage strengths of 12, 16, 24 and 32 mg)

- 1999 to 2004 - Additional Palladone submission cycles with approvable Letters issued on12/29/99; 9/13/02; 7/16/04. Not Approvable letter on 10/4/01

- September 9-10, 2003 - FDA Advisory Committee to address the Risk Management Program for Palladone
    - AC Recommendations
        - Use of Phased Roll Out
        - Development of a system to collect and analyze data from the surveillance program
        - Educate physicians regarding risks of opioids in general and Palladone in particular

- September 24, 2004 – FDA approved Palladone capsules for the management of persistent, moderate to severe pain in opiate-tolerant patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time.
    - Risk Management Program (RMP) to include
        - Labeling
            - Package Insert
            - MedGuide
        - Education
            - Professional Labeling
            - Healthcare Professional Education
            - Patient and Caregiver Education
        - Surveillance
            - Monitoring for significant safety issues, with initiation of specific interventions when monitoring reveals a safety issue and evaluation of the effectiveness of those interventions
    - Additional Commitments
        - Launch Program
            - Sales Force Training and Product Promotion
            - Limited Rollout Proposal with Evaluation Metrics
    - Other components of RMP
        - Policies, procedures and interventions dealing with material handling and supply chain integrity

        - Participation in or support of broad-based coalitions seeking systems solutions leading to appropriate use and reduced abuse and diversion of scheduled analgesics.
    - Reports
        - Expedited Safety Reporting and In-transit cargo theft within 15 days of receipt
        - Monthly and quarterly reports

- November, 2004 – Purdue conducted Palladone in-vitro "dissolution" testing as part of the Abuse Liability Assessment
    - Evidence of dose-dumping *in vitro*

- November, 2004 – Purdue conducted Palladone in-vivo alcohol interaction study to follow up results of in-vitro testing. The results of study as follows:
    - Cmax of Palladone was increased in relation to the concentration of alcohol co-administered (4, 20, 40% concentrations tested) an average of six (6) times greater with 40% alcohol than with water
    - Range was 2-16 fold increase with alcohol
    - Tmax was shorter with increasing alcohol concentrations (mean Tmax with 40% alcohol =1.68 hours, with water =9.4 hours)

- July, 2005 – FDA concluded the following:
    - Co-ingestion of Palladone with alcohol effectively defeats the extended-release formulation, resulting in dose dumping
    - Defeat of the Palladone extended-release mechanism is likely to be unintentional (as opposed to the crushing or chewing that is necessary to produce dose dumping for other extended-release opioids)
    - The volume of alcohol necessary to produce dose dumping is within a reasonable range for an alcohol drinker (120 mL = 4 ounces of 40% ethanol)
    - The specific warnings in the label may not be adequate to mitigate this safety risk

- July, 2005 – Agency meeting with Purdue

- July, 2005 – FDA issued a Healthcare Professional Alert regarding Alcohol-Palladone Interaction
    - PK data indicated that the co-ingestion of Palladone and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone
    - These elevated levels may be lethal, even in opioid-tolerant patients

- July, 2005 – Purdue agreed to voluntarily suspend sales and marketing of Palladone in the United States

Exalgo™ History – Key Milestones

- December 28, 1999 – Knoll Pharmaceuticals submitted NDA to FDA for Dilaudid CR® (Hydromorphone HCl 8, 16, 32 and 64 mg), an opioid analgesic in an oral, controlled-release formulation using the OROS® technology system for the proposed indication of analgesia for moderate to severe pain

- October 27, 2000 – FDA issued Knoll Pharmaceuticals an approvable letter informing that the NDA could not be approved due to several deficiencies including the need for one adequate and well-controlled Phase 3 clinical trial showing efficacy in the setting of moderate to severe pain

- The NDA was subsequently transferred to the ALZA Corporation (a subsidiary of Johnson and Johnson) who changed the name from Dilaudid CR® to OROS® Hydromorphone HCl

- April, 2007 –Neuromed Pharmaceuticals (Neuromed) acquired the rights to the NDA

- August, 2007 – the Agency granted a Special Protocol Agreement for the key efficacy study for the NDA

- October 5, 2007- NDA was transferred to Neuromed for Exalgo™ (Hydromorphone HCl 8, 16, 32 and 64 mg) an opioid analgesic in an oral, controlled-release formulation tablet using the OROS® technology system for the proposed indication of analgesia for moderate to severe pain.

- January 22, 2008 – FDA provided written response to Neuromed regarding their questions pertaining to the development program for Exalgo and their planned complete response

- August 8, 2008 – Pre-submission meeting was held between FDA and Neuromed regarding format and content needed to address the deficiencies of the Approvable letter

- May, 2009 – Complete response for Exalgo™ NDA was submitted by Neuromed

Drug Abuse Warning Network

The Drug Abuse Warning Network (DAWN) provides information on some of the medical consequences of substance use, misuse, and abuse that manifest in visits to hospital emergency departments. DAWN records substances associated with drug-related emergency department visits; provides a means for monitoring drug misuse and abuse patterns, trends, and the emergence of new substances; assesses some of the morbidity associated with drug misuse and abuse; and generates information for national, State, and local drug policy and program planning. DAWN is also a tool that is increasingly being utilized for postmarketing surveillance and risk management for the pharmaceuticals regulated by the Food and Drug Administration (FDA). DAWN is the responsibility of the Office of Applied Studies, a Federal statistical unit within the Substance Abuse and Mental Health Services Administration (SAMHSA).

A new data collection protocol was introduced for DAWN in 2003. The new design addressed many longstanding limitations associated with DAWN data. Because virtually every feature of DAWN changed with the redesign, data from 2004[1] and beyond are not comparable to data from 2002 and prior years.

DAWN relies on a national probability sample of non-Federal, short-stay, general hospitals that operate 24-hour emergency departments. Hospitals are oversampled in selected metropolitan areas and divisions, and a remainder sample covers hospitals in the remainder of the U.S. Based on data from sampled units, national estimates of drug-related emergency department visits for the U.S. are produced annually.

DAWN estimates for 2006 are based on a sample of 544 eligible hospitals, with 160 (28% to 70%) responding in oversample areas and 45 (23%) responding in the remainder area. Estimates reflect adjustments for the stratified sample design, unit nonresponse, and nonresponse within a facility. Whether an oversample area stands alone in the national estimate depends on its response rate and the potential for nonresponse bias. At this time, comparisons over time are available only for 2004, 2005, and 2006.

In addition, authorized users in DAWN member hospitals; Federal, State, and local public health agencies, including SAMHSA and FDA; and pharmaceutical firms receive access to the raw DAWN case data, in de-identified form, as the DAWN cases are submitted. This surveillance of sentinel events is possible through a secure, Internet-based query system called DAWN *Live!*

To collect the data, each hospital emergency department that participates in DAWN has one or more reporters who review emergency department medical records retrospectively to find DAWN cases. Cases reported to DAWN include emergency department visits caused by or related to drug use for patients of any age. The drug use must be recent; chronic effects and history of drug abuse are not reportable. Visits related to drugs used for therapeutic purposes, as well as drug misuse and abuse, are all included.

[1] Data from 2003 represent a transition year that is not comparable to prior or subsequent years.

For each reportable visit, demographic, visit, and drug characteristics are abstracted from the medical record. Each DAWN visit is classified into one of eight case types: drug-related suicide attempt, those seeking detoxification or substance abuse treatment services, underage alcohol use (with no other drug involved), adverse reactions to pharmaceuticals taken as prescribed, overmedication when the dose of a prescription or over-the-counter medication or dietary supplement was exceeded, malicious poisonings, accidental ingestions when a drug was used accidentally or unknowingly, and all others, including explicit drug abuse. This classification and the drugs reported to DAWN are used to derive analytic subgroups (e.g., for visits involving illicit drug use, alcohol use, or nonmedical use of pharmaceuticals) for a variety of purposes and audiences. Other data items characterize drug-related visits in terms of diagnoses or disposition.

DAWN captures very detailed drug information. As many as 16 drugs plus alcohol are reported for each DAWN case. Drug-related emergency department visits often include multiple drugs, on average, 1.6 drugs per visit. For adults, alcohol is reportable only when present with another reportable drug; for minors, alcohol is always reportable. Drug information is captured at the level of detail present in the medical record. The same drug may be reported to DAWN by brand, generic, chemical, street, or nonspecific name, depending on the completeness and specificity of information in the medical record. Training and automated rules prompt DAWN reporters to use all available documentation in the medical chart to record drugs by their most specific names (e.g., OxyContin, when documented as such, instead of oxycodone), not to record the same drug by different names (e.g., heroin and opiates), and to exclude current medications unrelated to the visit. Estimates are published at the generic level (e.g., acetaminophen-hydrocodone), for specific ingredients (e.g., dextromethorphan), or by drug category (e.g., opiates/opioids, benzodiazepines). Estimates attributed to particular brand or trade names (e.g., Concerta®) are generally not published.

Since data for DAWN are extracted from a retrospective review of medical records, no patients or health care providers are interviewed. Health care settings within the hospital but outside of the emergency department, or emergency facilities outside of hospitals, are not covered. Laboratory findings to detect the presence of a drug are not recorded for DAWN cases, although each drug report has an associated indicator for whether the drug was confirmed by toxicology testing. Only the patient's own drug use is considered, a patient’s intent to misuse or abuse a drug is not a factor in the DAWN case determination, and source of the drug is not captured because it is so rarely available in medical records. Repeat visits by the same individual cannot be linked together. Visits due to chronic conditions associated with a history of drug abuse are explicitly excluded. While DAWN does not collect direct identifiers, such as patient name, the content of the case data does render the data individually identifiable, and individually identifiable data are protected by Federal law from disclosure without consent.

DAWN does not measure the prevalence of drug abuse in the population, and external factors unrelated to the level of drug abuse in the population may contribute to the likelihood that a person presents to a hospital emergency department for a drug-related problem. For example, the availability of health insurance and/or other sources of care may influence whether an individual seeks care in an emergency department. Purity, experience, or other factors related to the physiological effects of drugs may affect whether a condition occurs to give rise to an emergency department visit.

DAWN also collects data on drug-related deaths reviewed by medical examiners and coroners (ME/Cs) in selected metropolitan areas and selected States. The death investigation jurisdictions that participate in DAWN do not constitute a statistical sample nor is every jurisdiction within a metropolitan area necessarily a participant. As a result, extrapolation of drug-related deaths to the Nation as a whole is not possible, and metropolitan area totals are only possible if all jurisdictions within the area participate. The number of jurisdictions that participate in DAWN varies from year to year. In 2003, the last year for which mortality data have been published, 122 jurisdictions in 35 metropolitan areas and 126 jurisdictions constituting six States participated in DAWN. The case criteria and data collection procedures for drug-related deaths mirror those used in emergency departments. Causes and manner of death are captured, in lieu of case type and diagnoses.

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

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.[i] 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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[i] 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 N	*Share* %	Retail TRxs N	*Share* %	Retail TRxs N	*Share* %
TOTAL MARKET	179,690,966	100.0%	192,502,779	100.0%	201,757,684	100.0%
Immediate Release	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%
Extended Release	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 N	*Share %*	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**179,658,813**	***100.0%***	**192,314,065**	***100.0%***	**201,569,753**	***100.0%***
Immediate Release	**164,214,355**	***91.4%***	**175,188,401**	***91.1%***	**183,144,243**	***90.9%***
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%*
Extended Release	**15,444,458**	***8.6%***	**17,125,664**	***8.9%***	**18,425,510**	***9.1%***
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	***Share***
	N	***%***
hydromorphone	**4,935,659**	***100.0%***
GP/FM/DO	861,279	*17.5%*
INTERNAL MEDICINE	757,399	*15.3%*
ANESTHESIOLOGY	523,792	*10.6%*
EMERGENCY MEDICINE	291,976	*5.9%*
UNSPEC	256,866	*5.2%*
ORTH SURG	244,788	*5.0%*
PHYSICAL MEDICINE & REHAB	221,864	*4.5%*
PHYSICIAN ASSISTANT	186,918	*3.8%*
NURSE PRACTITIONER	175,888	*3.6%*
ONCOLOGY	172,662	*3.5%*
All Others	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* %
hydromorphone	**2,042**	***100.0%***
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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/s/

PATTY A GREENE
08/21/2009

LAURA A GOVERNALE
08/21/2009
Cleared for AC background package

MEMORANDUM

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

Date: August 21, 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 report
2) In vitro abuse liability studies
3) Clinical Study Report: NMT 1077-301
4) Narratives "Patients of Interest" in Clinical Study NMT 1077-301
5) Clinical Study Report: C-2004-022-00
6) Draft labeling text

Background

This review provides conclusions to the Division of Anesthesia, Analgesia, and Rheumatology Products regarding the abuse potential of Exalgo (hydromorphone HCl) ER Tablets.

Knoll Pharmaceuticals submitted the New Drug Application (NDA) 21-217 for OROS® hydromorphone to FDA on 28 December 1999. Knoll received an Approvable Letter from the FDA on 27 October 2000, which contained deficiencies in the Chemistry, Manufacturing, and Controls (CMC), non-clinical, and clinical areas. Subsequent to receipt of the Approvable Letter, the NDA was transferred to the ALZA Corporation, a subsidiary of Johnson & Johnson. The NDA was further transferred to Neuromed

Pharmaceuticals following their acquiring the US rights to the product. The Sponsor is not seeking any claims or labeling statements about the physical properties of its extended release formulation.

Review

The Controlled Substance Staff (CSS) in CDER has reviewed and analyzed an extensive amount of data provided by the Sponsor, as well as information available about the abuse potential of hydromorphone from the scientific literature and data sources such as the Drug Abuse Warning Network (DAWN). The specifics of our review are not detailed here because of space limitations.

Conclusions

- As noted by several recent scientific articles, hydromorphone has a higher abuse potential than most other opiate drugs.[1, 2]
- Extended-release formulations of hydromorphone (like Exalgo) contain several times more opioid in a single dose than the immediate-release formulations (e.g., Dilaudid, 2, 4, and 8 mg). Therefore, Exalgo may pose a relatively higher risk for abuse and overdose than most of other opioids.
- The human bite force (102-133 lbf[3]) is great enough to crush an OROS Hydromorphone tablet. Since crushing the tablet defeats the controlled release mechanism and results in immediate-release characteristics, use of Exalgo increases the potential safety risks, including overdose or abuse.
- Abuse of Exalgo by the intravenous route is lethal because of hydromorphone toxicity as well as polyethylene oxide 2000K-induced cardiac necrosis and inflammation. (See Table 1).
- In clinical study NMT 1077-301, we note a considerable amount of test drug unaccounted for by some subjects who completed the trial and those who discontinued in both phases of the study. This may be predictive of the likely occurrence of diversion after the drug is approved and marketed.
- Overall, this product has a high abuse potential and has the same safety concerns observed by other similar extended release highly potent opioid drug products that are abused and diverted.

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[1] Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend. 2008 Dec 1; 98(3):191-202. Epub 2008 Jul 7.

[2] Hill JL, Zacny JP. Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. Psychopharmacology (Berl). 2000 Sep;152(1):31-9

[3] Pounds of force.

Table 1: Comparative Lethal Doses of Various Polyethylene Oxide Polymers and Hydromorphone Hydrochloride

Test Article	Species	Effect and Dose (mg/kg)
POLYOX 200K [a]	Rats, Single dose iv	LD50 = > 120
POLYOX 2000K [b]	Rats, Single dose iv	LD50 = 6
POLYOX 200K	Rats, Repeat dose (14 days) iv	LD50 = > 90
POLYOX 2000K	Rats, Repeat dose (14 days) iv	LD50 = 3.75
Hydromorphone HCl	Mouse, Single dose iv	LD50 = 55
	Mouse, Single dose sc	LD50 = 120
	Rat, Single dose sc	LD50 = 51
	Rabbit, Single dose iv	LDLo = 2.5
	Cat, Single Dose iv	LDLo = 3.0
Hydromorphone (Release from Palladone w/ Alcohol)	Human, oral	Potentially fatal dose = ~ 0.5 (32 mg total dose)
Polyethylene Glycol (PEG)		
PEG 200	Mouse, Single dose ip	LD50 = 11,800
PEG 1000	Mouse, Single dose ip	LD50 = 3,100
PEG 1000	Human, Single Dose iv [c]	NOAEL = ~15 (1g dose)
PEG 6000	Human, Single dose iv [c]	NOAEL = ~15 (1g dose)
PEG 3350 (Golytely)	Human, Single dose iv [d]	NOAEL = ~ 1,000 (23 g total dose)

a Content in a 64 mg OROS Hydromorphone tablet = 138 mg (2.3 mg/kg/60 kg patient)

b Content in a 64 mg OROS Hydromorphone tablet = 103 mg (1.7 mg/kg/60 kg patient)

c Excretion studies

d Unintentional injection, 4 year old girl, estimated body wgt~20 kg

Note: This Table is from "5.3.5.4. Abuse Liability Assessment" page 13.