CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-217

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	March 1, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	21217
Applicant Name	ALZA Corporation
Date of Submission	Original: December 28, 1999 AE: October 27, 2000 Resubmission: May 22, 2009
PDUFA Goal Date	March 1, 2010
Proprietary Name / Established (USAN) Name	Exalgo Hydromorphone HCl Extended Release
Dosage Forms / Strength	8 mg, 12 mg, 16 mg tablets
Proposed Indication	Management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Cross-discipline Team Leader	Ellen Fields, M.D., M.P.H.
Primary Medical Officer Review	Elizabeth Kilgore, M.D.
Statistical Reviews	Jonathan Norton, Ph.D., Dionne Price, Ph.D.
Pharmacology Toxicology Reviews	BeLinda Hayes, Ph.D., Dan Mellon, Ph.D.
CMC Reviews	Yong Hu, Ph.D., Prasad Peri, Ph.D.
Clinical Pharmacology	Wei Qui, Ph.D., Suresh Doddapaneni, Ph.D.
Controlled Substance Staff	JianPing Gong, M.D., Ph.D., Lori Love, M.D., Ph.D., Michael Klein, Ph.D.
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OSE/DMEPA	Anne Crandall, PharmD, Melina Griffis, R.Ph.
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SEALD	Debbie Beitzell, BSN

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
SEALD=Safety Endpoints and Labeling Development

1. Introduction

Hydromorphone is potent mu-agonist opioid analgesic that was first marketed in the U.S. in the 1920s. It is currently marketed in both approved and unapproved immediate-release formulations. The Dilaudid 8 mg formulation (NDA 19-892) was approved in 1992, followed by the 2 mg and 4 mg strengths in 2007. Palladone, an extended-release formulation of hydromorphone, was approved in 2004, but was withdrawn from the market in 2005 when data became available that demonstrated extensive dose-dumping when the drug was ingested with alcohol. This 505(b)(1) application for a novel extended-release formulation of hydromorphone was originally submitted in 1999 by Knoll Pharmaceuticals. An Approvable letter was issued in 2000 that delineated multiple CMC deficiencies, the absence of carcinogenicity studies in the application, and the fact that the clinical data in the application failed to demonstrate efficacy. A single, adequate and well-controlled study demonstrating efficacy was stated as the requirement for a complete response. The Division's decision to allow a single study in this setting, a policy which remains in place today, was based on the fact that single studies of extended-release (ER) formulations of opioids had been deemed adequate to support the approval of 505(b)(2) applications that referenced an approved IR

formulation. The basis for this policy is that when an opioid analgesic with established efficacy is referenced the only additional information necessary to establish the efficacy of the ER formulation is data demonstrating that the new formulation does not interfere with the ability of the drug substance to provide analgesia. The Division determined that, from a regulatory perspective, it would be unacceptable to hold a 505(b)(1) application to a different standard if the applicant was able to provide reference to an approved IR product. Knoll owned the approved application for the 8 mg Dilaudid product which would allow them to reference that application in support of efficacy.

Ownership of this NDA was subsequently transferred to Abbott Laboratories, then Alza, and finally to Neuromed in 2004. However, ownership of the parenteral and IR-formulation Dilaudid products was transferred to Purdue Pharma in 2007. Alza had obtained right of reference to the Purdue applications prior to the transfer to Neuromed. However, that right of reference was specific to Alza. Thus, the current applicant could no longer rely on the known efficacy and safety of the IR products without either a specific letter of authorization from Purdue Pharma, or by referencing Dilaudid in a 505(b)(2) application. The latter would require patent certification; however, a late patent was listed for NDA 19-892 that does not expire until November 2020. On February 5, 2010, Neuromed notified the division that they planned to transfer the application to Alza and that Alza will then have right of reference to the Dilaudid applications. On February 16, 2010, the Agency received a letter from Neuromed Pharmaceuticals that had transferred the ownership of and all rights to NDA 21-217 to Alza Corporation effective as of February 12, 2010. This change in ownership now allows right of reference to the Purdue applications.

After approval of a Special Protocol Assessment for their proposed efficacy study, successful completion of that study, and upon reaching agreement with the Division that the carcinogenicity studies could be conducted as a post-marketing requirement for reasons described below in Section 4, the sponsor submitted this complete response to the Approvable letter on May 22, 2009.

Additional outstanding issues which have been resolved in order to allow approval of the application include removal of the 32 mg dose and final agreement on the REMS and the product labeling. In addition, recent changes in our thinking regarding studies of opioid analgesics in pediatric patients required further discussion with the Pediatric Review Committee (PeRC) in order to determine whether efficacy studies will be required or waived for pediatric patients ages 2 through 17 years. That discussion has resulted in agreement that those studies may be waived.

2. Background

The applicant has provided adequate responses to the CMC deficiencies outlined in the Approvable letter and adequate data to demonstrate product quality. They have also provided adequate evidence of safety and efficacy for Exalgo when it is used according to the product label and have agreed to the completion of carcinogenicity studies as a post-marketing requirement. One of the other outstanding issues was the development of an adequate REMS

to address the high abuse potential of this product. Hydromorphone has an established history as a sought after drug of abuse based on numerous sources, including clinical abuse liability studies. The Exalgo formulation is particularly concerning due to the high doses incorporated in the ER tablets. (b) (4) Palladone was approved with a risk management plan that included a phased marketing rollout intended to evaluate the abuse of the product in the community before extensive prescribing occurred. This concept was supported by the members of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) who attended a meeting at which that product's application was discussed prior to its approval. The approach, however, was never evaluated as the product was pulled within a few months of marketing due to the dose-dumping with alcohol mentioned above.

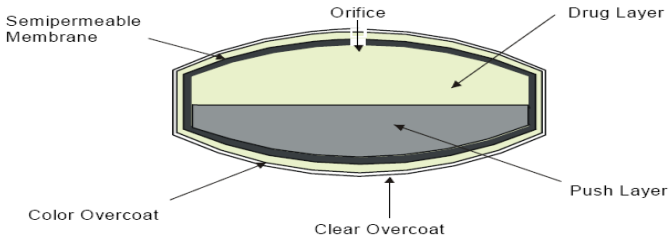
This application was also presented to the ALSDAC during the course of our review. A complete discussion follows below in Section 9. At that meeting, the members expressed a variety of opinions regarding the risks of and potential risk mitigation strategies for Exalgo. Neuromed presented an extensive REMS program that included numerous Elements to Assure Safe Use (ETASU). A clear consensus and recommendation from the committee was not achieved.

The review team agrees that a REMS is necessary to assure that the benefits of the product outweigh the risks. However, as this product falls into the class of extend-release and long-acting potent opioids, the REMS requested by the Division is the interim REMS that the Agency is applying to this class of products until the final REMS for those products has been established. The interim REMS consists of patient education in the form of a MedGuide and prescriber education required of the sponsor as an element to assure safe use. However, the review team has also concluded that this REMS will not adequately mitigate the risk of the 32 mg dose due to the large quantity of hydromorphone in those tablets, the high potency of hydromorphone and the fact that hydromorphone rates highly in all measures of abusability. Approval of the 32 mg dose would require a much more restrictive REMS. Therefore, we have requested that the sponsor remove that dose from the current application. They may then request approval of the dose once adequate data has been collected in the post-marketing environment to assure that the lower doses are not causing an increase in safety concerns related to the products potency and abusability, or submit an application for the dose with a REMS that adequately restricts its use. On February 11, 2010, the sponsor submitted a letter notifying the Agency that they were no longer seeking approval of the 32 mg strength tablet and appropriate changes were made to the product labeling.

3. CMC

The numerous CMC deficiencies delineated in the Approvable letter included insufficient information on the manufacturing of the drug substance, insufficient data on the acceptance criteria for the components of the drug product and in-process controls, and inadequate drug product specifications. The applicant provided data in this complete response to address each of these deficiencies. Drs. Hu and Perry have found the data to be adequate to support a recommendation for approval.

The Exalgo drug product is formulated as with the Oros® Push Pull Technology and is manufactured by Alza Corporation.



Additional CMC data for the new 12 mg tablets has been found acceptable by the review team. Stability data submitted to the application has been reviewed and a 30-month shelf life for the 8 mg tablets and a 36-month shelf life for the higher strength tablets have been found to be acceptable. All facility inspections have been completed and found to be acceptable. The applicant has agreed to perform microbial testing for drug product on stability for the first three commercial batches. I agree with the review team that no outstanding CMC issues remain which would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following summary from page 2 of Dr. Mellon's supervisory review summarizes the rather complicated pharmacology/toxicology review history for this application:

> NDA 21-217 (then referred to as Dilaudid CR) was originally submitted to the FDA on December 29, 1999 (receipt date) by Knoll Pharmaceuticals as a 505(b)(1) application. The product was originally developed under IND (b) (4) Dr. Kathy Haberny, the original pharmacology toxicology reviewer, reviewed a 30-day repeat-dose toxicology study in the dog with the drug product formulation, a fertility and early embryonic development study in the rat, embryo-fetal development studies in the rat and rabbit, pre- and postnatal development study in the rat, and three genetic toxicology studies for hydromorphone (the standard ICH battery). Dr. Haberny's 2000 review of NDA 21-217 notes that the pharmacology, safety pharmacology, pharmacokinetics and acute and chronic toxicity of hydromorphone were reported in the literature and cited in the original NDAs for Dilaudid (NDA 19-892 and 19-034) and referenced for the original 21-217 NDA submission (in 1999). She recommended the NDA was approvable pending agreement on the final product labeling and agreement to conduct the carcinogenicity assessment for hydromorphone hydrochloride post marketing. Dr. Dou H. Jean, the pharmacology toxicology supervisor at that time, concurred with Dr. Haberny. The NDA received an "Approvable" letter dated October 27, 2000 that listed multiple deficiencies. However, the only nonclinical deficiency listed in the Approvable letter was item 5, reproduced below:
>
> > No carcinogenicity studies of hydromorphone hydrochloride were submitted. Before the approval of the application you will have to conduct studies to evaluate the carcinogenicity of hydromorphone hydrochloride in two rodent species.
>
> The official meeting minutes from the post action meeting held December 7, 2000 contained the following question from Knoll and response from the Agency:

> 5. In several meetings prior to the December 1999 NDA submission, Knoll understood the Agency to be in agreement that carcinogenicity studies were not necessary for approval of this product. For example, the Division's 2 September minutes of the 4 August 1999 pre-NDA meeting state (p.2): "Carcinogenicity studies are not required at this time." It should also be noted that valid carcinogenicity data is a key "refusal-to-file" criteria, if not waived, for chronic indication NDAs. Knoll would appreciate clarification of the Division's rationale for this recent change in position.
>
> All new NDA's for chronic indication of opioids submitted after December 1999, require carcinogenicity studies data. This change in policy was implemented around the time of the Dilaudid NDA 21-217 submission, therefore the lack of carcinogenicity data was not considered a 'refusal to file" issue. The Division indicated that in the case of Dilaudid, the carcinogenicity studies have to be underway by the time of NDA submission, and that submission of final study reports could be considered a postmarketing commitment.

The carcinogenicity studies are, indeed, underway, thus allowing us to honor the previous agreement. The applicant submitted new pharmacology, safety pharmacology, pharmacokinetic, and acute and chronic toxicology studies in their response to the Approvable letter (due to their having lost right of reference to the IR product applications) and Dr. Hayes did evaluate these studies. However, she only provided a formal review of the studies that were deemed pivotal to the application. As noted in Dr. Mellon's supervisory review, studies that were not deemed necessary for safety or labeling were not formally reviewed. However, Dr. Mellon further notes that all nonclinical studies necessary for approval of a 505(b)(1) application and labeling were submitted by the Applicant and reviewed by the review team with the exception of the agreed upon post marketing carcinogenicity study requirements. Therefore, whether the sponsor of this application ultimately did or did not have right of reference to the Purdue applications was not pertinent to the pharmacology/toxicology review team's assessment of approvability.

I agree with the review team that there are no outstanding pharmacology or toxicology issues that would preclude approval at this time.

5. Clinical Pharmacology/Biopharmaceutics

Although there were no clinical pharmacology or biopharmaceutics deficiencies noted in the Approvable letter, the applicant provided 19 clinical pharmacology studies in their resubmission. Thirteen of these studies were either already included in the original application or were included in the IR product applications. The specific special population PK studies that exclusively used the IR formulation and were previously submitted to the IR product applications are studies on the effect of hepatic impairment, renal impairment, age, and gender. In the original submission of this NDA, sub-group analysis on the effect of gender was conducted and no clinically meaningful PK differences were seen. With respect to age effect, PK data on the elderly was not available with Exalgo. However, this is not a significant deficiency as the clinical database included an adequate number of elderly subjects and did not raise any concerns regarding the efficacy and safety of Exalgo in the elderly. With respect to the effect of hepatic and renal impairment on the PK of Exalgo, since this product will be titrated to effect with careful dose individualization, these data are not necessary for approval. In addition, further studies will not be required as the sponsor does now have right of reference

to these data. The other six studies had not previously been submitted to the Agency. Dr. Qiu focused her review on five of those studies (b) (4)

A dosage form equivalence study found that two of the 4 mg tablets are bioequivalent to one 8 mg tablet. However, the applicant is not planning on marketing the 4 mg tablets at this time. Single- and multiple-dose relative bioavailability studies documented that a single dose of the 16 mg Exalgo tablet provides an equivalent AUC to a 4 mg IR tablet administered every 6 hours under fasting conditions, and multiple doses of the 16 mg Exalgo tablet provide equivalent exposure at steady state to a 4 mg IR tablet administered every 6 hours under fasting conditions. There were considerably less plasma level fluctuations in Cmax and Cmin with the Exalgo formulation as would be expected. A food effect study demonstrated an absence of a clinically relevant effect. An alcohol interaction study demonstrated an absence of dose-dumping with concomitant ingestion of Exalgo tablets and alcohol. The results of an abuse liability study are discussed below under Clinical Safety, Section 8.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics issues which would preclude approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The single efficacy study submitted with the complete response, Study NMT 1077-301 (Study 301) was a multicenter, randomized, placebo-controlled, double-blind, randomized withdrawal design trial which compared Exalgo to placebo in opioid-tolerant adults with chronic low back pain (CLBP). All subjects were converted from their opioid analgesic to Exalgo and titrated to an effective dose between 12 and 64 mg over 2 to 4 weeks. They were then randomized 1:1 to receive either their current effective dose of Exalgo or placebo. The double-blind phase of the study lasted 12 weeks. The placebo subjects were gradually tapered from Exalgo during the first 14 days of the double-blind phase. IR hydromorphone was the only rescue analgesic permitted.

The primary outcome measure was the change from Baseline to Week 12 of the double-blind phase or the final visit in the subject's pain intensity score on an 11-point numerical rating scale. During the conversion/titration phase of the study, of the 447 subjects who received at least one dose of study drug, 39% discontinued, 13% due to adverse events and 12% due to lack of efficacy. Fifty-one percent of the Exalgo subjects and 67% of the placebo subjects discontinued during the double-blind phase. Twelve percent of the Exalgo subjects and 30% of the placebo subjects discontinued due to lack of efficacy. Nine percent of the placebo subjects discontinued due to greater than allowed use of rescue analgesia. Seventy percent of the subjects who discontinued were among those receiving 64 mg of Exalgo per day with the most common reasons for discontinuation in this group being adverse events and non-

compliance at ~19% each. Discontinuations due to withdrawal symptoms were more common in the placebo subjects, as would be expected, at 5% compared to 2% of the Exalgo subjects.

The following table, reproduced from page 10 of Dr. Fields' review, summarizes the results of the primary outcome analysis:

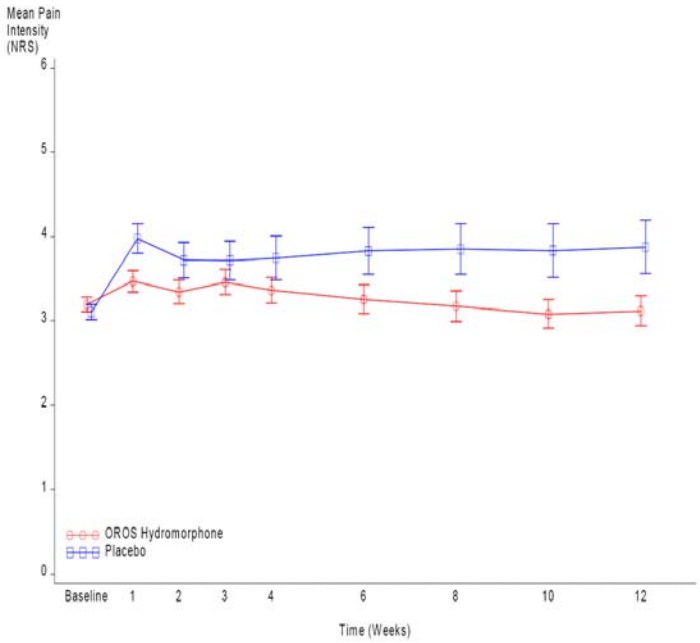
Numeric Rating Scale (NRS) Pain Intensity Change from Baseline to Week 12 (or final visit) in Double-blind Phase (ITT Population); Study 301

Statistic[a]	OROS® Hydromorphone	Placebo	P-value[b]
Baseline[c]			
N	133	133	
Mean	3.2	3.1	
Median	3.3	3.3	
Range (min, max)	0, 6	0, 6	
Visit 11/final visit (Week 12)[d]			
N	133	133	
Mean	3.8	4.8	
Median	3.6	4.8	
Range (min, max)	0, 9	0, 9	
Change from Baseline			0.000007
N	133	133	
Mean	0.6	1.7	
Median	0.2	1.6	
Range (min, max)	-5, 5	-3, 7	

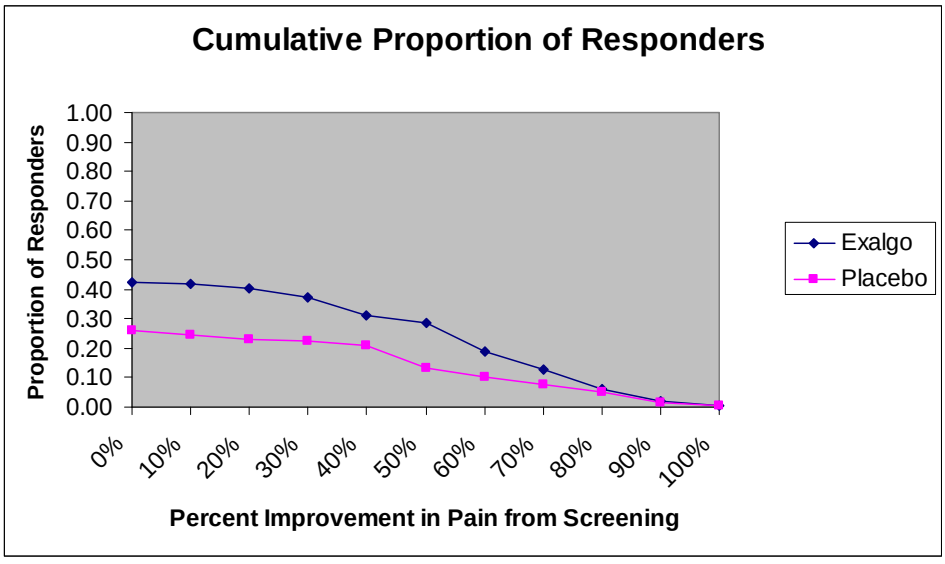
[a]This is an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain).
[b]P-value from test for significant treatment difference using Cochran-Mantel-Haenszel chi-square test comparing change from Baseline after adjusting for Baseline value using ranks.
[c]Mean of the patient diary measurements in the week prior to randomization.
[d]Patients with missing weekly patient diary data due to premature withdrawal had their value at final visit imputed based on the reason for discontinuation.

ITT=intent-to-treat; max=maximum; min=minimum

The applicant also provided the following graph (reproduced from page 11 of Dr. Fields' review) which displays the pain curves over the full 12-week double-blind phase of the study:



In addition, the sponsor performed a cumulative responder analysis the results of which are displayed in the following graph, reproduced from page 12 of Dr. Fields' review:



The use of rescue medication was similar between the two treatment groups, with most of the subjects in each group using rescue medication. Secondary endpoint analyses were generally supportive of the findings on the primary outcome analysis.

8. Safety

The reader is referred to Dr. Kilgore's thorough review of the clinical safety of this product. As the safety profile appears to be typical of a potent, extended-release opioid other than a gastrointestinal concern related to the Oros formulation, I will briefly summarize the findings.

A total of 2,335 subjects received at least one dose of Exalgo in Phase 2 and 3 clinical studies. Of those 2,335 subjects, 420 were exposed for greater than 6 months and 141 for greater than 12 months. There were 64 deaths in the exposed subject population. Drs. Kilgore and Fields have determined that only one of those deaths might plausibly be directly or indirectly related to exposure to Exalgo, with the rest of the deaths clearly related to progression of underlying disease or to other acute medical/surgical causes. The one patient who they determined might have died at least partially due to Exalgo exposure was a 40-year old woman with a history of diabetes, asthma, obesity, arthritis, stomach ulcer, and abdominal surgery with the subsequent development of adhesions resulting in chronic pain. The patient died on Day 12 of treatment with Exalgo 24 mg per day. She had also been treated with prednisone and naproxen. The autopsy confirmed cause of death was an intra-abdominal abscess with peritonitis and perforation of the cecum due to necrotizing pseudomembranous colitits. Dr. Kilgore concluded that the use of Exalgo may have decreased gastrointestinal motility and contributed to the perforation. I concur with this assessment; however, this toxicity is not specific to Exalgo, but is a risk well known with the chronic use of any opioid medication.

Serious adverse events (SAEs) were reported in 10% of the subjects who received Exalgo in the combined controlled and open-label studies. Dr. Kilgore has determined that these events were consistent with the known safety profile of opioid drugs. The following table, reproduced from page 14 of Dr. Fields' review, summarizes the SAEs reported for subjects in the controlled clinical studies:

Serious Adverse Events: Controlled Clinical Studies

MedDRA System Organ Classification	Exalgo N = 1572 (%)	Placebo N = 466 (%)
At least 1 SAE	69 (4.4)	8 (1.7)
GI	15 (1.0)	3 (0.6)
General disorders	11 (0.7)	1 (0.2)
Infections and infestations	9 (0.6)	2 (0.4)
Nervous system disorders	7 (0.4)	1 (0.2)

Again, these events and the rates of occurrence are consistent with those seen in subjects in clinical studies of opioid drug products in general. Twenty-three percent of subjects receiving Exalgo and 5% of placebo subjects discontinued during the controlled studies. The most common adverse events resulting in discontinuation were nausea, constipation, vomiting and somnolence. The most commonly reported adverse events were constipation, nausea, vomiting, somnolence, dizziness and headache. There were no clinically significant or unexpected findings in the reported laboratory values or vital signs.

Serious gastrointestinal effects have been associated with the use of the OROS formulation in other drug products. These events have included bezoar formation, obstruction, perforation and constipation. Dr. Kilgore analyzed the safety data for this application specifically looking for events which might have been related to the OROS formulation. She documented 15 SAEs that might have been related to this formulation, including gastric outlet obstruction, abdominal pain, bowel obstruction, bezoar formation and severe nausea, vomiting and constipation. However, she and Dr. Fields noted that it is not possible to clearly attribute these events to the formulation as they may have been due to underlying disease of chronic opioid induced constipation.

9. Advisory Committee Meeting

The following summary of the advisory committee meeting held last year to discuss this application has been reproduced from page 15 of Dr. Fields' review:

> A Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee was held on September 23, 2009 to discuss this submission. The following questions were posed to the committees:
>
> 1. Discuss where Exalgo lies in the spectrum of risk for abuse, including abuse-related overdose and death, compared to other opioid drug products.
>
> 2. Based on your assessment of the risk associated with abuse of Exalgo, discuss which of the following options would be appropriate for risk management:
>
>   a. A program similar to Onsolis, including registration for physicians and patients
>   b. An opioid class-like program, including physician education and registration, but no patient registry and, in the short term, an interim REMS pending the larger opioid class program as was done with Embeda
>   c. A unique program
>
> The general consensus of the Committees was as follows:
>
> 1. In terms of abusability, Exalgo appears similar to Oxycontin. There was no real consensus as to where Exalgo may lie along a continuum, but it was felt that it has a high abuse potential.
>
> 2. Exalgo should have a REMS which fits into the opioid-class REMS. The Committee felt that the REMS proposed by the Applicant contained several important features.
>
> 3. The model of a restricted marketing roll-out was presented to the Committee by the Agency. Many Committee members felt that this model may be an effective strategy for Exalgo.

10. Pediatrics

While the applicant's initial Pediatric Plan was determined to be unacceptable to the review team, a revised plan was submitted during the review period. This plan included a waiver request for studies in pediatric patients less than 2 years of age and a deferral request for pediatric patients ages 2 to 17 years. The applicant proposed to attempt to develop an age

appropriate formulation that would retain the extended-release characteristics of the OROS formulation for pediatric patients under the age of 7 years. The review team found this plan acceptable and the plan was approved by the PeRC. However, based on recent changes in our thinking about the requirements for studies of opioid analgesics in pediatric patients ages 2 to 17 years, the review team recommended that it would be acceptable to waive the efficacy studies for this age group. This matter was discussed with the PeRC and they concurred with our recommendation.

11. Other Relevant Regulatory Issues

There are no other outstanding regulatory issues.

12. Labeling

Agreement on the product label has been reached with the sponsor. Appropriate changes to the labeling were made to reflect the removal of the 32 mg strength tablets and the change in ownership to Alza Corporation.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The sponsor has provided adequate data to support the efficacy and safety of Exalgo when used according to the product labeling and under the conditions of a REMS, but only for the 8 mg, 12 mg and 16 mg tablets. Due to the high dose, the high potency of hydromorphone, and the well-established abusability of hydromorphone, we have determined that the 32 mg dose should be removed from this application. The sponsor may submit a supplement for that dose once adequate data have been collected to demonstrate that there has not been an increase in safety concerns with the lower doses in the post-marketing environment. Alternatively, they may submit an application for the 32 mg dose with a REMS that will have restrictions for its use that are adequate to mitigate the risks inherent to that dose. The sponsor has provided a letter acknowledging that they are no longer seeking approval of the 32 mg dose at this time and appropriate changes have been made to the product labeling.

- Post-marketing Risk Management Activities

  The sponsor submitted a REMS in response to the Agency's request. However, the REMS that they submitted was determined to be inappropriate for this drug product. As such, the Agency issued a second REMS request letter which

aligned the proposed REMS for this product with the other extended-release potent opioid drug products. That REMS was submitted and has been reviewed and found to be acceptable.

- Post-marketing Study Requirements

  - Completion of the following deferred pediatric studies will be required under PREA:

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

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

  - Completion of the ongoing carcinogenicity study in mouse.

  - Completion of the ongoing carcinogenicity study in rat.

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

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

/s/

BOB A RAPPAPORT
03/01/2010