

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-217s000

**CROSS DISCIPLINE TEAM
LEADER REVIEW**

Cross-Discipline Team Leader Review

Date	February 23, 2010
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA	21-217 Complete Response
Applicant	Alza
Date of Submission	May 22, 2009
PDUFA Goal Date	November 22, 2009
Proprietary Name / Established (USAN) names	Exalgo/Hydromorphone HCl Extended Release
Dosage forms / Strength	Tablet/8mg, 12mg, 16mg, 32mg
Proposed Indication(s)	Management of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time
Recommended:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
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.
DDMAC	Mathilda Fienkeng, Twyla Thompson, Sangeeta Vaswani
DSI	Susan Leibenhaut, M.D.,
OSE/DMEPA	Anne Crandall, PharmD, Melina Griffis, R.Ph.
OSE/DRISK	Jeanne Perla, Ph.D., Sharon Mills, BSN, RN, Mary Willy, Ph.D.
SEALD	Debbie Beitzell, BSN

Cross Discipline Team Leader Review

1. Introduction

This application is a complete response submitted by Neuromed to the Approvable Letter for NDA 21-217 issued on October 27, 2000. They are seeking approval of EXALGO (hydromorphone) Extended-Release Tablets for once daily administration 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. The original NDA was submitted on December 29, 1999 as a 505(b)(2) application relying in part on the Agency's previous findings of efficacy and safety for Dilaudid immediate-release hydromorphone.

2. Background

Hydromorphone is a potent opioid analgesic that was first introduced into the market in the early 1920's. It is a μ -receptor agonist that is currently marketed in the US in various approved and unapproved dosage forms. Approved versions of the immediate-release tablets (Dilaudid) are available in 2, 4, and 8mg doses. The 8mg tablets were approved in 1992, followed by the lower strengths in 2007. Palladone, an extended-release hydromorphone product was approved in September 2004, but was withdrawn from the market in July, 2005 due to extensive dose-dumping when ingested with alcohol.

The controlled-release product that is the subject of this NDA uses the OROS® system and has been formulated as 8, 12, 16, 32 and 64-mg tablets. The OROS® system consists of a tablet, which comprises a bilayer core coated with an insoluble cellulosic rate-controlling membrane. An orifice drilled into the membrane allows the "push-pull" technology to release hydromorphone in a controlled manner over approximately 24 hours.

The original NDA for this product was submitted by Knoll Pharmaceuticals in December, 1999. An Approvable letter was issued on October 27, 2000 that delineated Chemistry, Manufacturing and Controls (CMC), preclinical, and clinical deficiencies. The CMC deficiencies included insufficient information on the manufacture 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 preclinical deficiency was the absence of carcinogenicity studies in the submission. The clinical deficiency was that the data submitted in support of the NDA failed to demonstrate efficacy for the intended indication. The Applicant was told that an adequate and well-controlled study, with multiple dosing of the to-be-marketed formulation, in the setting of moderate to severe pain, would be necessary to establish the efficacy of the product.

The NDA was subsequently transferred to Abbott, then Alza, and ultimately Neuromed, in 2004. However, ownership of the parenteral and oral IR formulations of hydromorphone was transferred to Purdue Pharma in 2000. Thus, Neuromed does not have right of reference to the IR products without either a specific letter of authorization from Purdue Pharma, or 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 plan to transfer the application

to Alza and that Alza will then have right of reference to the Dilaudid applications. The application was successfully transferred to Alza on February 12, 2010.

In 2004, Alza submitted protocol NMT-1077-301 to assess efficacy in patients with chronic low back pain, which was accepted under a Special Protocol Assessment (SPA). The Applicant was informed at a meeting with the Division on August 8, 2008 that carcinogenicity studies could be conducted as a post-approval requirement. Comments on the plans for the Risk Evaluation and Mitigation Strategy were also provided.

This product, under the tradename, Journista, was approved in Denmark in 2004, and is currently marketed in nine countries in dosage strengths of 4, 8, 16, 32 and 64 mg.

This application contains complete reports for 20 clinical studies not included in the original 1999 NDA submission, including 11 pharmacokinetic studies, and nine Phase 2/3 clinical studies including the trial intended to support the efficacy of Exalgo. Preclinical study reports for genotoxicity, repeat dose toxicity in dogs and rats, and local tolerance studies were also included in this application.

3. CMC/Device

The CMC review was performed by Yong Hu, Ph.D. A secondary review was completed by Prasad Peri, Ph.D. The following is a summary of their reviews. The application addresses the deficiencies identified in the Agency's approvable letter. In addition, a new dosage strength (12 mg) is proposed and a new drug substance supplier, Noramco, has been identified.

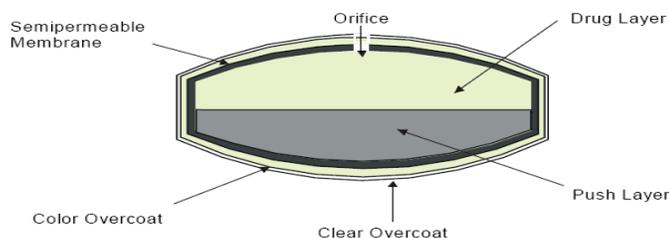
Drug Substance

The drug substance, hydromorphone hydrochloride, is a semi synthetic drug substance derived from oripavine which is obtained from plants. The previous source was (b) (4) and in this resubmission has been replaced by a new supplier: (b) (4). The (b) (4) drug substance is a white to almost white powder. It is freely soluble in water; slightly soluble in methanol and ethanol; (b) (4). The drug substance is (b) (4).

(b) (4) The chemistry, manufacture, and controls of hydromorphone hydrochloride are described in (b) (4) DMF (b) (4). The drug substance was deemed satisfactory according to the CMC reviews.

Drug Product

The drug product is an Oros® Push Pull Technology based extended-release tablet with a laser drilled orifice on one side. The side of the tablet where the orifice is located is distinguished from the other side by the color of the tablet. The orifice (b) (4) is where the drug comes out of the tablet inside the body. The tablet is to be administered as a whole without crushing or splitting. The drug product is manufactured at Alza® Corporation, CA.



There are five strengths: 8 mg (red), 12 mg (dark yellow), 16 mg (yellow), 32 mg (b) (4) and 64 mg (b) (4) of hydromorphone hydrochloride with different amounts of overages that are used for the 8, 12 and 16 mg strengths. The Applicant claims that overages are needed since some amount of drug is left over in the tablet. All strengths use micronized drug substance that is blended into the drug layer. The tablets are distinguished by their size, markings on the tablet and their color.

The drug product is manufactured through a series of unit operations involving (b) (4)

Specification of the drug product include: Appearance, Identification by IR and HPLC, Assay, Content uniformity (USP <905>), Dissolution, Moisture content, (b) (4) and Microbial Limits on stability. It was demonstrated that hydromorphone hydrochloride exhibited very low water activity (b) (4) along with some reports of antimicrobial activity and hence the potential of microbial growth is very low. The Applicant demonstrated that the drug product is compliant with microbial limits at release. A commitment to monitor the microbial content of the first three commercial batches of the 8 mg and 64 mg strength products is being sought.

Adequate stability data for the drug product has been provided to issue a 30 month shelf life for the 8 mg strength and 36 months for all other strengths (12 mg, 16 mg, 32 mg, and 64 mg per tablet).

The CMC review found the drug product to be satisfactory.

Additional Findings

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Post approval CMC agreement

The Applicant has agreed to perform microbial testing for drug product on stability (12, 24 and 36 months) for the low (8 mg) and high strength (64 mg) products for the first three commercial batches.

Overall Conclusion:

From a CMC perspective, the application is approvable. The Applicant has addressed the CMC deficiencies in the approvable letter of 27-Oct-2000 sufficiently, the CMC information for the new 12mg strength is adequate, and a biowaiver for the 12 mg strength is recommended by the Biopharmaceutics Review Team. The Applicant has also provided adequate comparability data to qualify the new drug substance supplier, (b) (4)

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was performed by BeLinda Hayes, Ph.D., with supervisory concurrence from Dan Mellon, Ph.D.

The Approvable Letter dated October 27, 2000, noted the following nonclinical deficiency: “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.” Special Protocol Assessments-Carcinogenicity were submitted to the Agency in October of 2005 and November of 2008 for the mouse and rat proposed 2-year carcinogenicity study, respectively. During the pre-NDA meeting on August 8, 2008, the Applicant proposed that the carcinogenicity studies be conducted as a post-marketing commitment, to which the Agency agreed, however the carcinogenicity studies must be underway at the time of NDA submission. Neuromed Pharmaceuticals confirmed that the rat (Study № 1678-002) and mouse (Study № 1678-001) carcinogenicity studies were initiated on March 18, 2009 and March 24, 2009, respectively.

The nonclinical development program outlined in this submission relies in part on the FDA’s previous findings of safety and efficacy of hydromorphone and nonclinical data in the published literature and submitted study reports. New study reports submitted with this application include genotoxicity, repeat-dose toxicity in dogs and rats, and local tolerance studies. Dr. Hayes found no new nonclinical safety issues relevant to this drug product.

Based on Dr. Dan Mellon’s review of the regulatory history and the information submitted by Neuromed as part of this response to the approvable letter, Neuromed has provided all studies necessary to ensure that this NDA submission can still be deemed a 505(b)(1) submission, even without a right of reference to the Dilaudid NDAs from a pharmacology/toxicology perspective..

Labeling changes to Section 8.1 (Pregnancy) were made to be consistent with other opioid labels. Section 13 (Carcinogenesis, Mutagenesis, and Impairment of Fertility) was amended to be consistent with the Dilaudid and Embeda labels pending the results of the ongoing carcinogenicity studies. (b) (4)

The ongoing carcinogenicity studies in the mouse and rat will be postmarketing requirements. There do not appear to be any preclinical issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was completed by Wei Qiu, Ph.D., with secondary concurrence from Suresh Doddapaneni, Ph.D. The following summarizes their review.

There were no clinical pharmacology deficiencies noted in the Approvable letter for Dilaudid CR. A total of 19 clinical pharmacology studies were included in this current submission, 13 of which were either submitted in the original NDA 21-217 or included in the NDAs for Dilaudid (hydromorphone hydrochloride Oral Liquid, NDA 19-891), Dilaudid (hydromorphone hydrochloride 8 mg Tablets, NDA 18-892), or Dilaudid HP (hydromorphone hydrochloride Injection, NDA 19-034). Six new studies were submitted as part of the Complete Response. The clinical pharmacology review focused on the following in vivo studies: dosage form equivalence study (C-2005-032), single dose relative BA and food effect study (42801-PAI-1008), multiple dose relative BA study (42801-PAI-1009), alcohol interaction study (C-2005-020), and abuse potential study (C-2004-022).

The findings of the clinical pharmacology team are as follows:

Dosage Form Equivalence: Two of the 4 mg tablets are bioequivalent to one 8 mg tablet. The sponsor is not proposing to market 4 mg strength at this time.

Relative Bioavailability (Exalgo ER tablet vs. Immediate Release (IR) Tablet):

Single dose: Single oral dose of the 16 mg Exalgo tablet provides equivalent AUC_t or AUC_{inf} of hydromorphone as the 4 mg IR tablet every 6 hours (q6h) under fasting conditions.

Multiple dose: Multiple oral doses of the once daily 16 mg Exalgo tablet provide equivalent exposure (AUC_{0-τ}) of hydromorphone as the 4 mg IR tablet q6h at steady state under fasting conditions. The plasma concentration fluctuation based on C_{max} and C_{min} values are significantly less for Exalgo compared to the IR tablet. The figure below from Dr. Qiu's review illustrates these findings.

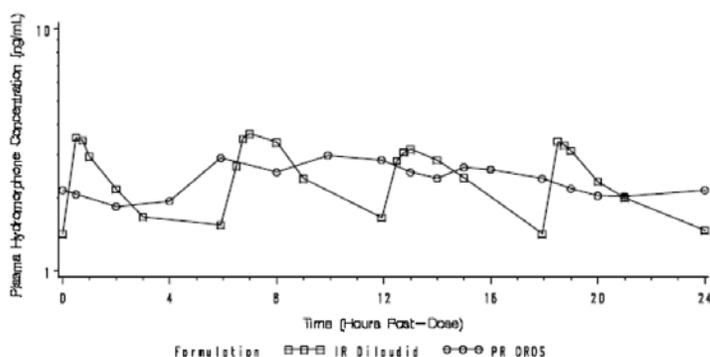


Figure 6 Mean Plasma Concentration-Time Profiles of Hydromorphone on Day 5 Following Multiple Oral Doses of 16 mg Exalgo Tablets and 4 mg Dilaudid Tablet Administered q6h Under Fasted Conditions in Healthy Subjects (Study 42801-PAI-1009).

Food Effect: Food does not affect the PK of Exalgo.

Alcohol Effect: The controlled-release property of Exalgo is maintained in the presence of alcohol and there is no ‘dose dumping’ of hydromorphone. The C_{max} values in the 3 alcohol treatments in the fasted state are higher than that in the 0% alcohol treatment, with mean geometric ratios of 117%, 131%, and 128% for the 4%, 20%, and 40% alcohol treatments, respectively. In the fed state, the mean geometric ratios are 114%, 114%, and 110%, for the 4%, 20%, and 40% alcohol treatments, respectively. The maximal increase in C_{max} observed in any individual subject is 2.5-fold in fasting condition and 2-fold under fed condition in the comparison of the 40% vs. 0% alcohol treatments. Although the in vitro release rate is slightly increased in the presence of 40% alcohol, the release characteristics were maintained.

Abuse Potential: Study C-2004-022 was a single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized, crossover study in healthy subjects who had a history of polydrug use and moderate opiate use, but were not dependent on opiates. It consisted of two phases, Phase A and Phase B. In Phase A, each subject received single doses of intact Exalgo 16 mg and 32 mg, Exalgo 8 mg crushed, hydromorphone 8 mg IR tablet, and placebo. If all treatments were well tolerated, subjects entered Phase B. In Phase B, subjects received single doses of Exalgo 64 mg and 8 mg IR hydromorphone tablet (active control).

Figure 1 from Dr. Qiu’s review shows the PK profiles for subjects who completed Phase A. Table 1 summarizes the PK parameters for subjects who completed Phase A and Phase B. In Phase A, the PK profile of crushed Exalgo 8 mg was similar to that of 8 mg IR tablet, with T_{max} values around 1.4 to 1.7 hours. The T_{max} values of different strengths of Exalgo intact tablets were 16 to 18 hours. The numerical trend of C_{max} values is 8 mg IR tablet > Exalgo 8 mg crushed > Exalgo 32 mg intact > Exalgo 16 mg intact. The PK profile of the IR 8 mg tablet is similar between Phase A and Phase B. In Phase B, the Exalgo 64 mg intact tablet has similar C_{max} as the 8 mg IR tablet.

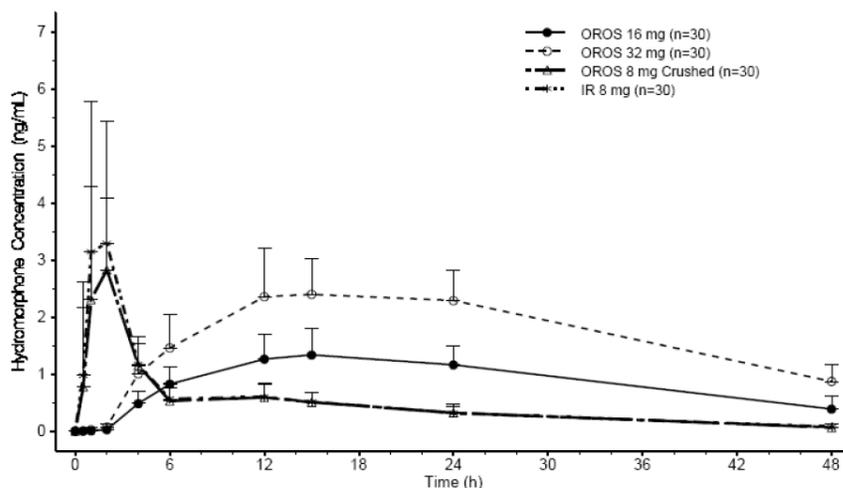


Figure 1 Mean (SD) Plasma Hydromorphone concentration Profiles (all subjects who completed Phase A)

Table 1 Mean (SD) Plasma Hydromorphone Pharmacokinetic Parameters

Parameter	Phase A (n = 30)				Phase B (n = 28)	
	8 mg IR tablet	Exalgo 32 mg	Exalgo 16 mg	Exalgo 8 mg crushed	8 mg IR Tablet	Exalgo 64 mg
Cmax (ng/mL)	4.86 (2.3)	2.79 (0.66)	1.50 (0.41)	3.67 (1.5)	5.00 (2.6)	4.43 (1.6)
Tmax (h)	1.43 (0.75)	17.0 (5.7)	16.0 (4.7)	1.74 (0.93)	1.49 (1.0)	18.3 (7.1)
T1/2 (h)	12.1 (4.0)	16.5 (2.9)	16.9 (5.3)	12.4 (3.4)	13.9 (6.1)	Not estimable
AUCt (ng.h/mL)	23.5 (7.5)	81.1 (15)	41.1 (11)	21.4 (6.9)	21.9 (6.6)	140 (46)
AUCinf (ng.h/mL)	25.7 (7.7)	101 918)	50.9 (14)	24.0 (6.5)	24.5 (6.3)	Not estimable

The pharmacodynamic aspects of this study will be discussed in Section X with the results of the CSS review.

According to the clinical pharmacology review team, there are no issues from their perspective that would preclude approval.

6. Clinical Microbiology

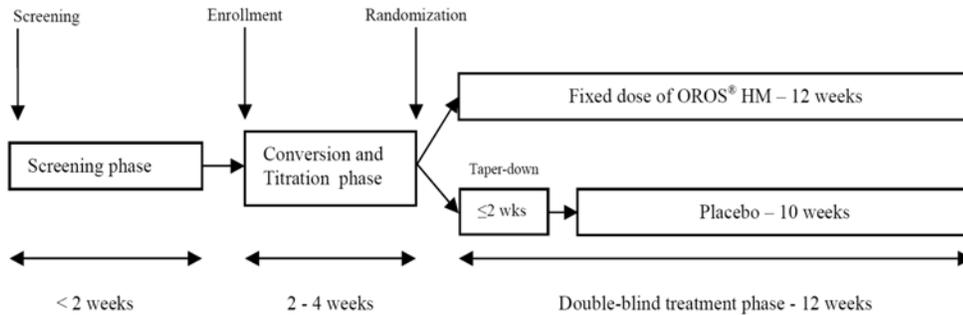
There is no clinical microbiology review for this product.

7. Clinical/Statistical- Efficacy

A full review of the Phase 3 trial submitted in support of efficacy was conducted by Dr. Elizabeth Kilgore, and the statistical review was conducted by Dr. Jonathan Norton. The following is a summary of their findings.

Study NMT 1077-301 (Study 301), was planned as a multi-center, randomized, placebo-controlled, double-blind study with a conversion and titration phase lasting 2 to 4 weeks, and a

double-blind phase lasting 12 weeks, in opioid-tolerant male and female patients aged 18 to 75 years with chronic low back pain, who have required at least 60 mg but not more than 320mg morphine equivalent per day for the prior two months for their CLBP. Eligible patients were to have been converted from their prior opioid to Exalgo and titrated to an effective dose (12mg to 64mg Exalgo) during the conversion/titration phase of the trial, then randomized 1:1 to receive either their effective dose of Exalgo or matching placebo. Placebo subjects were to have been gradually tapered from Exalgo during the first 14 days of the double-blind phase of the trial. Rescue medication (hydromorphone IR) was to have been allowed, however concomitant non-opioid analgesics were not allowed during the trial. The figure below from Dr. Kilgore’s review summarizes the design of the study.



Pain intensity scores as measured using an 11-point numerical rating scale were to have been collected at screening and at all visits, and in subjects’ daily diaries, along with secondary outcome measures. COWS and SOWS assessments were also performed throughout the double-blind treatment period to assess withdrawal symptoms. The protocol specified primary efficacy endpoint was the change from Baseline to Double-blind Week 12 or final visit in weekly mean pain intensity (PI) scores recorded in the patient diaries.

Four hundred and fifty-nine (459) patients were enrolled in the conversion and titration Phase, and 268 patients were randomized to the double-blind phase (134 patients to hydromorphone ER arm and 134 to the placebo arm). One patient randomized to receive hydromorphone ER did not report taking any study medication. Another patient, randomized to receive placebo, did not have Baseline values for the primary efficacy variable. Both of these patients were excluded from the ITT population. Therefore, the ITT population had 266 patients. A total of 110 patients completed the study (66 patients in the hydromorphone arm and 44 in the placebo arm).

One-hundred-seventy-nine patients (39%) who received at least one dose of study drug discontinued from the conversion and titration phase after receiving study drug. Adverse events (13%) and lack of analgesic efficacy (12%) were the most common reasons. A total of 158 patients dropped out during the double-blind phase, 68 (51%) in the Exalgo group and 90 (67%) in the placebo group. The most common reason for discontinuation in both groups was lack of analgesic efficacy (12% in the Exalgo group and 30% in the placebo group). Nine percent of the placebo group discontinued due to unacceptable rescue medication use. The majority of discontinuations (70%) were among patients receiving 64 mg of hydromorphone

ER per day. The most common reasons for discontinuation in this dose group were AEs and non-compliance (~19% each). Discontinuations due to withdrawal symptoms was more common in the placebo group than the Exalgo group during the double-blind phase, as would be expected (5% vs. 2%).

Protocol violations were balanced between the two treatment groups during the double blind phase, the most common reason being “inclusion criteria not met”. Of the 37 patients listed as not meeting the double-blind inclusion criteria, in all cases but one, the reason was that they had a pain score greater than four at the randomization baseline. Since these violations preceded randomization, in principle they do not undermine the efficacy analysis. Moreover, they were balanced across treatment arms.

The treatment arms were generally balanced demographically. Most subjects were Caucasian (84.6%). There were more males in the hydromorphone group (54.1%) but more females (54.9%) in the placebo group. The majority of subjects (94.0%) was under the age of 65 and had non-neuropathic low back pain (64.3%). The baseline mean pain intensity NRS scores were 3.2 in the Exalgo group and 3.1 in the placebo group.

The mean duration of exposure to study drug during the double-blind phase was 52.6 days for Exalgo compared to 38.6 days for placebo. Forty-five percent of Exalgo treated patients had at least 12 weeks exposure versus 25% in the placebo group. The most common final dose for all patients during the conversion and titration phase was 64 mg per day (22%).

The primary efficacy endpoint was the change from baseline to double-blind Week 12 (or last visit) in weekly mean pain intensity scores (based on the previous week’s mean daily pain intensity Numeric Rating Scale (NRS) scores recorded in patient diaries). The baseline pain score was defined as the average of the diary pain intensity (PI) NRS scores in the week prior to randomization. The analysis was based on the intent-to-treat population, which consisted of all study subjects who received at least one dose of study drug during the double-blind treatment period. The primary analysis agreed to in the SPA was analysis of covariance (ANCOVA). The independent variables in the model were to be treatment, site, and baseline pain score. The baseline pain was defined as the average of the diary values in the week prior to randomization. Missing values due to premature withdrawal were to be imputed as follows:

- For discontinuations due to apparent opioid withdrawal symptoms, the randomization baseline score would be carried forward. Note that the pain score carried forward is relatively low.
- For discontinuations due to an adverse event (AE), the screening pain observation would be carried forward (SOCF). This is a relatively high score.
- For other discontinuations, last-observation-carried-forward (LOCF) imputation would be used. The last observation was defined as the average pain score over the final week that the patient is in the study. This category included patients who discontinued due to excessive use of rescue.

If the Week 12 pain scores were missing but the patient did not discontinue, then LOCF was to be used. The analysis did not adjust for use of rescue medication by patients who stayed in the trial.

The analysis the Applicant submitted with the NDA however, was based upon a different statistical analysis plan (SAP) than was agreed upon as part of the SPA. In the new SAP, the effect of treatment center was removed from the ANCOVA model. Also, the analysis method used was to depend on whether the data violated certain assumptions. If any of the assumptions were violated, then the Applicant planned to use a non-parametric methodology. Details regarding this analysis may be found in Dr. Norton’s review.

The following table from the submission illustrates the results of the primary endpoint 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			
N	133	133	0.000007
Mean	0.6	1.7	
Median	0.2	1.6	
Range (min, max)	-5, 5	-3, 7	

^aThis is an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain).

^bP-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.

^cMean of the patient diary measurements in the week prior to randomization.

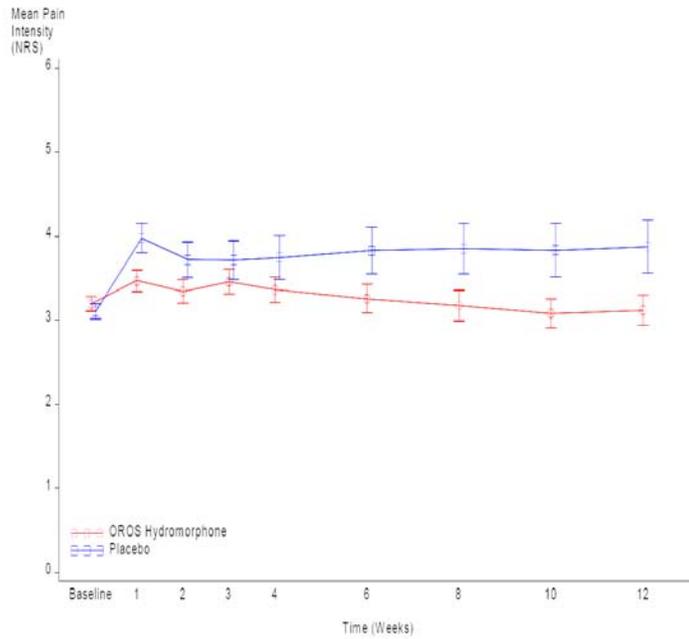
^dPatients with missing weekly patient diary data due to premature withdrawal had their value at final visit imputed based on the reason for discontinuation.

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

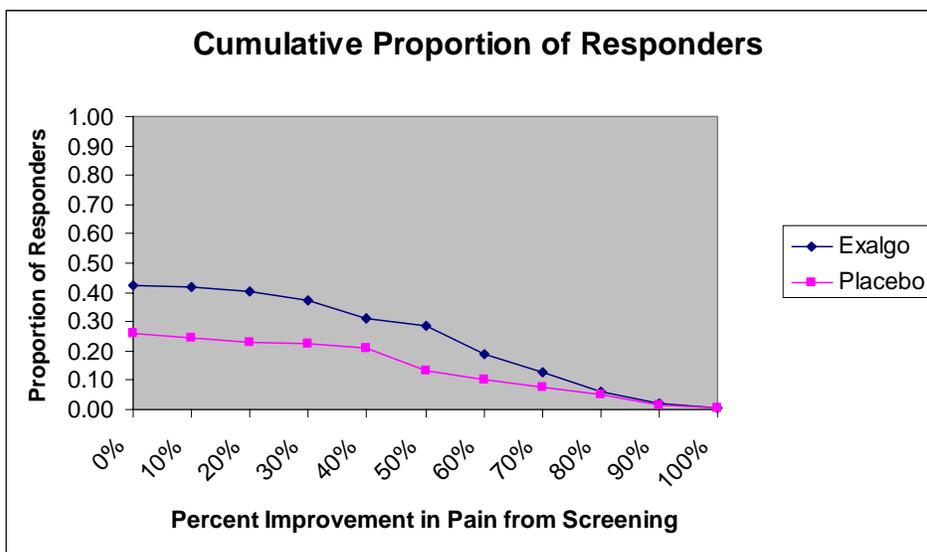
The Applicant’s analysis of the primary endpoint was significant (p<.001) in favor of treatment with Exalgo. Mean change from baseline in the hydromorphone treated group was 0.6 compared to the mean change from baseline for the placebo group of 1.7, resulting in a treatment effect of 1.1.

Dr. Norton was able to reproduce the Applicant’s analysis above. At the request of the statistical review team, the Applicant also carried out the SPA version of the primary analysis. Using the SPA analysis, the Applicant again found Exalgo to be statistically superior to placebo (p < .001), and this analysis was also verified by Dr. Norton.

The Applicant provided the following pain curve over the 12-week double-blind treatment period, showing a separation between the Exalgo and placebo groups.



In addition, a cumulative responder analysis was performed by the Applicant. In the Applicant’s responder analysis, missing pain scores were imputed at Week 12. However the Division’s policy has been to treat all patients who withdraw from analgesic trials as non-responders, based on the rationale that a withdrawal suggests that the patient was not benefitting from treatment, either due to lack of efficacy or adverse events. The responder curve below is from Dr. Norton’s review, in which dropouts were excluded from the analysis. The relatively low response rates reflect the high dropout rates, however a separation between treatment groups in favor of Exalgo is still evident at both the 30% (37% vs. 22% response) and 50% (28% vs. 13%) improvement in pain from baseline. With either cutoff, Exalgo was statistically superior to placebo using a chi-square test ($p < .01$).



Secondary endpoints that supported the primary analysis included change in pain intensity over the entire 12-week double-blind period, pain intensity score by visit, time to treatment failure, patient global assessment, Roland Morris Disability Score, and rates of discontinuation. Details regarding these analyses can be found in Dr. Kilgore's review.

Of note, use of rescue medication was similar in the two treatment groups: 96% for subjects in the Exalgo group and 97% for placebo subjects. Since subjects taking a weekly average of more than two tablets of rescue (2, 4, or 8mg tablets) after the first two weeks of the double-blind period were discontinued from the trial, there was a ceiling regarding the amount of rescue taken. Additionally, while less rescue in the Exalgo group would have been expected, it is common for patients on long-acting opioids to require immediate-release opioids for periods of exacerbations in their pain, or activity during the day that increases pain.

Dr. Norton performed subgroup analyses for the primary endpoint by age, race, and sex. There was a marginally significant interaction between age and treatment effect ($p = .09$), with patients under 55 tending to show a larger effect. The treatment effect did not significantly differ between genders. It was not possible to perform a meaningful test for an interaction with race due to the small number of non-Caucasian subjects.

Study 301 provided some support for once daily dosing of Exalgo, although daily rescue medication (weekly average <2 tablets/day) was required for almost all subjects in the Exalgo treatment group. As stated above, rescue use is common in patients receiving extended-release opioids. The range of Exalgo doses in Study 301 (12mg-64mg/day) reflects the varied requirement of patients, based on pain level, degree of opioid tolerance, and underlying condition.

The Applicant submitted five additional studies in support of efficacy that have been summarized by Dr. Kilgore in her review. They included two failed trials and three open-label trials. None were considered adequate, well-controlled trials to support efficacy.

As stated in the Approvable letter from the first NDA cycle, a single adequate and well-controlled study will be necessary to demonstrate the efficacy of Exalgo for the proposed indication. Study 301 has demonstrated efficacy for Exalgo based on analysis of the primary endpoint, change in pain intensity during the double-blind treatment period from baseline to Week 12, with a small but statistically significant treatment effect. The cumulative responder analysis supported these findings in that the proportion of responders the 30% and 50% cutoffs for improvement in pain intensity were also statistically significant in favor of Exalgo.

8. Safety

A full review of safety was conducted by Dr. Kilgore. The following is a summary of the findings from her review.

The ISS contained safety information from seven pooled uncontrolled studies, six pooled controlled studies, and 13 pooled Phase 1 studies (subjects were naltrexone blocked and therefore will not contribute to safety). Three PK studies in special populations, one abuse

liability study, and one acute pain study were not pooled. The pool of controlled studies contained patients who were opioid-tolerant, opioid-treated but non-tolerant, and opioid-naïve.

The exposure to Exalgo in terms of number of subjects, doses and duration are adequate. The safety database (pooled controlled and uncontrolled studies) submitted with the NDA consisted of a total of 2,335 patients who received at least one dose of Exalgo during Phase 2 and 3 clinical trials.

In the primary studies (those without extensions), the duration of treatment ranged from one day to approximately 65 weeks. The median daily dose was 16.0 mg (range: 0.2 to 895.7 mg). The duration of treatment in the extended studies ranged from 2.0 days to approximately 20 months. The median daily dose was 41.4 mg (ranging from 6 mg to 1,984 mg). There were 420 patients exposed >6 months and 141 patients exposed >12 months.

The proportion of females in the safety population was slightly greater than males, (56% vs. 45%) and the average age was 64 years. Over 90% of the population was Caucasian.

There were 64 deaths in the safety population (n=2335) in subjects who received Exalgo, the majority of which occurred in patients with malignancies and were associated with disease progression. There were no deaths reported in Phase 1 studies. Dr. Kilgore reviewed all death narratives and determined that none of the deaths were either definitely or probably related to study drug. She determined that one death may have been possibly related to study drug. The patient was a 40 year old female with a complex medical history including diabetes, asthma, obesity, arthritis, stomach ulcer, abdominal surgery and subsequent adhesions resulting in chronic pain. The patient received 24mg/day of Exalgo. She was also receiving prednisone and naproxen. On (b) (4) of treatment she expired. At autopsy the cause of death was stated as an intra-abdominal abscess with peritonitis and perforation of the cecum due to necrotizing pseudomembranous colitis. Dr. Kilgore determined that there were sufficient underlying issues to account for this death, however the use of opioids may have decreased GI motility and contributed to the perforation.

Serious adverse events (SAEs) were reported in 10% (240/2335) of subjects who received Exalgo in the pooled controlled and uncontrolled trials. Following thorough review, Dr. Kilgore determined that the events were consistent with the known profile of opioid drugs, and there did not appear to be an unusual pattern or increased frequency of these events that might suggest a problem specific to Exalgo. The frequency of occurrence of SAEs by System Organ Classification revealed that the GI system at 2.1% (49/2335) contained the highest percentage of patients reporting an SAE, followed by Infections and infestations at 1.9% (44/2335), and General disorders and administration site conditions at 1.8% (43/2335). The most common SAEs were nausea and vomiting, followed by pneumonia and chest pain.

The following table from Dr. Kilgore's review shows the rate of SAEs in controlled studies, comparing treatment groups. There was a very low rate of SAEs in patients receiving placebo in the controlled studies (1.7%, 8/466). Also note the rate in patients receiving Exalgo was less than half that in the pooled controlled/uncontrolled studies. The likely explanation is that a large proportion of patients in the uncontrolled studies had chronic pain due to malignancies,

whereas the controlled studies included mostly patients with osteoarthritis and chronic low back pain who were less ill than the patients with malignancies, and consequently had fewer SAEs.

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)

Twenty-three percent of subjects receiving Exalgo in the controlled studies discontinued due to AEs, compared with 5% of placebo treated subjects. The most common reasons for discontinuation were opioid-related adverse events including nausea, constipation, vomiting and somnolence.

The use of the OROS formulation in other drug products has been associated with serious gastrointestinal adverse events including bezoar formation, obstruction, perforation, and constipation. Fifteen serious adverse events that might be attributable to the use of the OROS technology have been summarized by Dr. Kilgore on pages 136-151 of her review. Gastric outlet obstruction, abdominal pain, bowel obstruction, bezoar formation, and severe nausea, vomiting and constipation could be associated with the OROS formulation. However, no clear-cut determination of causality has been made regarding these events, and they could also be attributable to underlying disease or chronic opiate consumption.

The overall incidence of adverse events in subjects exposed to Exalgo in the controlled and uncontrolled studies was approximately 80%. The most commonly reported AEs (>10%) were those known to be associated with opioid use, and included constipation, nausea, vomiting, somnolence, dizziness, and headache. The overall incidence of AEs was noted to be slightly higher in subjects 65 years of age and older compared to those less than 65.

There were no clinically significant or unexpected changes in laboratory values or vital signs attributable to Exalgo.

Overall, the safety profile for Exalgo appears to be similar to other potent opioids with the exception of possible serious gastrointestinal adverse events related to the OROS delivery system.

9. Advisory Committee Meeting

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

The initial Pediatric Plan submitted with the NDA, which was not acceptable to the Division, requested a waiver for studies in pediatric patients less than (b) years of age and a deferral for the children ages (b) to 17 years, and proposed that an (b) (4) (b) (4). A revised plan was submitted on September 10, 2009, and included a waiver request for studies in pediatric patients less than 2 years, and a deferral for pediatric patients aged 2 to 17 years. Studies would include pharmacokinetic studies, adequate and well-controlled efficacy and studies in opioid-tolerant pediatric patients with chronic pain requiring around the clock opioid treatment. The Applicant agreed to attempt to develop an age-appropriate formulation that would retain the extended-release characteristics of the OROS formulation for pediatric patients less than 7 years of age. The following study descriptions and timeline were submitted to the Agency.

Timeline for Proposed Pediatric Studies

Study Title	Protocol Submission Date	Study Start Date	Completion Date	Final Study Submission Date
A Phase 1, PK Study in Children (Ages 7-17) who are Opioid Tolerant with Chronic Pain	(b) (4)			
(b) (4)				

Pain				
A Phase 1, PK Study in Children (Ages 2-<7) who are Opioid Tolerant with Chronic Pain	(b) (4)			
(b) (4)				

The Pediatric Plan was approved by PeRC on October 14, 2009. However, based on recent changes in the Division’s thinking about the requirements for studies of opioid analgesics in pediatric patients ages 2 to 17 years, findings of efficacy for opioids in the adult population can be extrapolated to pediatric patients. An administrative update stating that efficacy studies in children ages 2-17 years are not necessary for Exalgo was sent to the PeRC and Dr. Lisa Mathis concurred. The final pediatric plan to be completed as post-marketing requirements is as follows:

1. A Phase 1, Pharmacokinetic and Safety Study in Children (Ages 7 – 17) who are Opioid Tolerant with Chronic Pain

Date for protocol submission: 10/31/10
 Date for study start: 3/31/11
 Study completion: 3/31/12
 Final study report submission: 7/31/12

2. A Phase 1, Pharmacokinetic and Safety Study in Children (Ages 2 – < 7) who are Opioid Tolerant with Chronic Pain

Date for protocol submission: 3/31/12
 Date for study start: 9/30/12
 Study completion: 9/30/13
 Final study report submission: 1/30/14

3. Other Relevant Regulatory Issues

Division of Scientific Investigations

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for Protocol NMT 1077-301, the single clinical efficacy trial conducted to support approval of Exalgo. Two study sites were selected based on enrollment of large numbers of study subjects. Sites for Dr. Arifulla Khan and Dr. Douglas Young were inspected.

The major finding at Dr. Khan’s site was that the central laboratory did not have the capability to perform testing for tramadol and fentanyl early in the study (these medications were not allowed during the study) as part of the urine drug tests. Subjects taking these drugs were excluded from the study by history, however these drugs were not initially included in the urine drug screens both at screening and during the trial. A memo from the (b) (4) laboratory dated April 7, 2008 stated that testing for these drugs would be possible after that date. Only

abnormal drug screen values were reported to the sites. Of note, this occurred at all clinical sites and was not unique to this site. Three-hundred ninety-one subjects were screened at all sites prior to April 7, and of these 44 had tramadol or fentanyl listed as prior medications. These subjects were distributed throughout all study sites. Twenty-three of these patients were randomized, and six were tested during the trial, which leaves 17 subjects who were not tested for these drugs. Due to the relatively small number of subjects left untested (17/266), and the fact that the subjects were randomized into treatment groups, this issue is not expected affect the efficacy findings from this study.

Other findings at Dr. Kahn's site included that there was no under reporting of adverse events and the primary endpoint data were verifiable. There were a small number of minor protocol violations regarding inclusion criteria that would not be expected to affect the reliability of the data generated from this site. DSI concluded that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

The inspection of Dr. Young's site showed that there was no under reporting of adverse events and the primary endpoint data were verifiable. A small number of deviations were noted that would not be expected to affect the reliability of the data from this site. DSI concluded that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Controlled Substance Staff Consult

The Controlled Substance Staff (CSS) conducted a review of the abuse liability of Exalgo, including its relative potency to other opioids, drug extractability studies, animal toxicology studies, an alcohol interaction study, the results of a human abuse potential clinical trial (Study C-2004-022), and a drug accountability analysis. Please refer to Dr. Gong's review for details.

The following are the conclusions of the CSS review:

- Hydromorphone is relatively more potent than most of other opiate drugs with regard to analgesia and abuse potential.
- Extended-release formulations of hydromorphone (like Exalgo) contain several times more opioid in a single dose than an immediate-release formulation. Therefore, it poses relatively higher risks for abuse and overdose than most of other opioids, (b) (4)
- (b) (4)
The human bite force is great enough to crush an OROS hydromorphone tablet. Since crushing the tablet defeats the controlled release mechanism and results in immediate-release characteristics, hydromorphone HCl ER Tablets will increase the potential risks for overdose or abuse in those seeking to defeat the extended-release system.
- Administration of OROS hydromorphone with up to 40% alcohol appears not result in "dose dumping". However, individuals may experience a substantial increase in hydromorphone peak (C_{max}) concentration. So, administration of OROS hydromorphone with alcohol will pose more safety risks for overdose.
- Animal study results showed that OROS hydromorphone would carry the liability of serious polyethylene oxide 2000K-associated systemic effects, especially necrosis and

inflammation of cardiac tissues. Therefore, abuse of the product by the intravenous route is potentially lethal following repeated intravenous injections of non-lethal doses.

- The PK profile of crushed OROS hydromorphone 8 mg was similar to that of hydromorphone 8 mg IR. Thus, 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.
- In a human abuse potential pharmacology study, 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.
- We note a high level of drug unaccountability in some subjects who completed the trial and those who were discontinued in both phases in clinical study NMT 1077-301. This is predictive of the likely occurrence of diversion after the drug is approved and marketed.

According to CSS, taken together, these findings suggest that expanded use of this product after marketing raises serious safety concerns, and are likely to result in significant abuse and diversion that further impacts the public health and safety.

4. Labeling

The proprietary name, Exalgo, was reviewed and found acceptable by DMEPA and DDMAC. DMEPA also provided recommendations regarding the labeling including the carton and container that would provide increased clarity and minimize medical errors. DDMAC reviewed the label and made recommendations regarding revisions of promotional language and language that appears to minimize the risks associated with this product. The label was reviewed by SEALD who made recommendations regarding PLR formatting.

Exalgo is unique among the extended-release oral opioid products in that all dosage strengths are for use only in opioid-tolerant patients. This will be clearly stated throughout the label, including within the Boxed Warning. A Medication Guide will be included in the Exalgo labeling as part of the Risk Evaluation and Mitigation Strategy.

5. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend Exalgo (include doses) for Approval 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.

- Risk Benefit Assessment

Exalgo has satisfactorily been shown efficacious for the proposed indication in one adequate and well-controlled efficacy trial in opioid-tolerant adult patients with chronic low back pain. A single efficacy trial is sufficient in this setting, since the application (when originally owned by Alza) relies in part on previous findings of safety and efficacy for Dilaudid (IR Hydromorphone), and as per the Approvable Letter for Dilaudid CR, the Applicant was told to conduct a single efficacy trial. However, the ownership of this NDA was transferred from Alza to Neuromed, and according to OCC who reviewed documents related to this transfer, the

right of reference to the Dilaudid NDAs did not transfer to Neuromed. On February 12, 2010, the NDA was successfully transferred back to Alza, who is allowed to reference the Purdue immediate-release hydromorphone applications.

There are no new or unexpected safety signals associated with Exalgo, and its safety profile is similar to that of other extended-release opioid analgesics. However, the OROS technology has been associated with bezoar formation and intestinal obstruction, especially in patients with preexisting gastrointestinal pathology, with previously approved products that utilized OROS. The combination of an opioid, known to be associated with decreased in GI motility, and the OROS formulation may also be associated with obstruction. The safety database for Exalgo included 15 gastrointestinal adverse events that could be associated with the OROS formulation, although none could be assigned definite causality. Information regarding the risks associated with the OROS formulation are included in the Exalgo label.

Exalgo is unique among other extended-release oral opioids in that all dosages are for use only in opioid-tolerant patients. The lowest labeled starting dose is 12mg once daily, which is equivalent to a daily dose of approximately 60 mg of morphine sulfate. The Exalgo label clearly states in the Box Warning and throughout the label that this product is for use only in opioid-tolerant patients. The Applicant has requested marketing for the 8mg, 12mg, 16mg, and 32mg tablets. However taking into account the issues brought up by the Controlled Substance Staff regarding the likeability and abusability of hydromorphone, and the potential for unintended overdose resulting from inappropriate prescribing, the Division has made the decision to not approve the 32mg strength at this time. In order for this strength to be approved, the Applicant must show that Exalgo is being prescribed appropriately (i.e., proper patient selection, proper dose selection) over a period of time. 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 Division received a correspondence from the Applicant on February 11, 2010, stating that they are no longer seeking approval of the 32mg strength of Exalgo, and are seeking approval only for the 8, 12, and 16 mg strengths

In terms of the risk of abuse, misuse, and overdose, hydromorphone is well known to be a highly “likeable” opioid, and the rates of abuse of immediate-release hydromorphone are relatively high compared to other immediate-release opioid products. CSS completed an extensive review of the relevant studies submitted in this application, and concluded that extended-release formulations of hydromorphone, like Exalgo, contain several times more opioid in a single dose than an IR formulation, and therefore pose a relatively higher risk for abuse and overdose than other opioids, especially if the controlled-release formulation is defeated by crushing or extraction. Hydromorphone (b) (4) pharmacokinetic profile of crushed Exalgo 8mg is similar to that of 8mg of immediate-release hydromorphone. These facts, combined with the results of the single-dose human abuse liability study and the high level of drug unaccountability in the clinical trials, suggest that Exalgo has high abuse potential.

Although Exalgo is associated with risks of abuse, misuse, and overdose, it is also an important addition to the armamentarium for the treatment of chronic pain. Additionally, the risks appear similar to other already approved extended-release opioids, and the degree to which Exalgo may be more or less abusable than other extended-release opioids is unknown. In order to mitigate the risks associated with these products, the Agency is working with Industry to develop a class-wide Risk Evaluation and Mitigation Strategy. Exalgo will be included in the products that adopt the class-wide REMS, and until then, an “interim REMS” will be part of this approval, the details of which are described in the next section.

- Recommendation for Postmarketing Risk Management Activities

Due to the risks of abuse, misuse, overdose and death associated with extended-release opioids, the Agency has determined that extended-release opioids must have a Risk Evaluation and Mitigation Strategy (REMS). The development of a class-wide opioid REMS that will encompass all extended-release opioids and methadone for the pain indication is currently in progress. The advantage of the class-wide REMS compared to individual REMS for each product is the lessening of the burden to providers and patients from a single system. The Agency is working with industry and other stakeholders to assess and develop an optimally designed REMS. Until then, each newly approved extended-release opioid product will have an “interim REMS” that is similar to the Risk Management Plans that are already in place for the previously approved opioids in this class. To that end, the interim REMS will be comprised of a Medication Guide, a Communication Plan (letters to providers, pharmacies, and medical societies, and a brochure), and a Timeline for REMS assessments.

The Applicant submitted a REMS in response to the Agency’s request. However, the REMS that they submitted was determined to be inadequate 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. The final submitted REMS consists of a Medication Guide, a Dear Healthcare Professional letter, an educational brochure, and the package insert. This REMS has been reviewed by the Division and OSE and has been found acceptable.

- Recommendation for other Postmarketing Study Requirements

Pediatric studies

1. A Phase 1, Pharmacokinetic and Safety Study in Children (Ages 7 – 17) who are Opioid Tolerant with Chronic Pain

Date for protocol submission: 10/31/10

Date for study start: 3/31/11

Study completion: 3/31/12

Final study report submission: 7/31/12

2. A Phase 1, Pharmacokinetic and Safety Study in Children (Ages 2 – < 7) who are Opioid Tolerant with Chronic Pain

Date for protocol submission: 3/31/12
Date for study start: 9/30/12
Study completion: 9/30/13
Final study report submission: 1/30/14

Other PMRs

Carcinogenicity study in mouse, (currently ongoing):

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

Carcinogenicity study in rat, (currently ongoing)

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

- Recommended Comments to Applicant

The CMC team provided the following comment regarding an agreement reached between the Agency and the Applicant:

- Microbial testing will be performed on the drug product for stability (12, 24 and 36 months) for the low (8 mg) and high strength (64 mg) products for the first three commercial batches.

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/

ELLEN W FIELDS
02/23/2010