CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204031Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Addendum

Date	February 24, 2014
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Review Addendum
NDA #	204031
Applicant	Mallinckrodt, Inc
Date of Submission	May 28, 2013
PDUFA Goal Date	November 28, 2013
Proprietary Name / Established (USAN) names	Xartemis XR /oxycodone HCl and acetaminophen
Dosage forms / Strength	Oxycodone 7.5 mg and acetaminophen 325 mg ER tablets
Proposed Indication(s)	Management of (b) (4) acute pain where the use of an opioid analgesic is appropriate
Recommended:	Approval

1. Introduction

NDA 204031 was submitted by Mallinckrodt Inc. (the Applicant) as a 505(b)(2) application for COV795 (oxycodone hydrochloride and acetaminophen) extended-release tablets for the management of (b) (4) acute pain. A CDTL memo was filed in DARRTS on November 7, 2013 that reviewed the submission for Xartemis XR including a summary of the Controlled Substance Staff (CSS) review of the in vivo and in vitro data submitted in the original NDA submission by the Applicant to the support abuse deterrent (AD) properties of Xartemis XR and labeling language regarding these properties. The conclusion reached at that time was that the Applicant had adequately demonstrated safety and efficacy of Xartemis XR for the treatment of acute pain, however the in vitro and in vivo data submitted with the NDA were not sufficient to support the abuse deterrent properties or labeling language for Xartemis XR, as determined by CSS.

The Applicant believes that Xartemis XR offers AD features for various populations of abusers for three major routes of abuse; oral, (b) (4) and intravenous (IV), and that their studies demonstrate that these properties are meaningful. They submitted an amendment to the NDA (eCTD seq#0014 (SD-15) received on November 19, 2013), that contained in vitro data (b) (4) of Xartemis XR. The Division made the decision to extend the review clock based on this major amendment, to allow time for review of the additional data that supported the AD properties of Xartemis XR so that if in fact this data was compelling, the product would be approved and labeled with AD properties. At the time of the amendment submission, the Division felt that this was a possibility.

Submissions Related to Abuse Deterrence of Xartemis XR Received after November 7, 2013

Date Received	Sequence #	Reports
November 8, 2013	0012	• (b) (4)
November 19, 2013*	0014	•
December 23, 2013	0016	•
January 10, 2014	0017	•

- Major amendment to NDA, triggered review clock extension

The major focus of this CDTL addendum is the CSS review of the additional AD information submitted by the Applicant in the above NDA amendments, and the clinical relevance this information.

Throughout this review, Xartemis XR and MNK795 will be used interchangeably.

2. Background

Refer to my CDTL review dated November 7, 2013 for details regarding the clinical development of Xartemis XR.

3. Abuse Deterrent Issues

(b) (4)

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7. Labeling

(b) (4)

Indication

The Applicant's proposed indication and limitations of use have been revised to better align with the current indications for the ER/LA opioid analgesics, in order to assure safe use and prescribing. The indication and limitations of use as they appear in the approved Xartemis XR label are as follows:

> XARTEMIS XR is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.
>
> Limitations of Use
> Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, reserve Xartemis XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate.

Neonatal Opioid Withdrawal Syndrome

These sections will be revised in all immediate and extended release opioid analgesics in order to adequately inform prescribers of this the potential for this condition in infants of mothers who have prolonged use of opioids.

> **5.3 Neonatal Opioid Withdrawal Syndrome**
>
> Prolonged (b) (4) use of XARTEMIS XR during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
>
> **8.1 Pregnancy**
> *Clinical Considerations*
> *Fetal/Neonatal Adverse Reactions*
> Prolonged maternal use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see Warnings and Precautions (5.3)].

Risks Specific to Xartemis XR

The following language was added to section 9.2 under the above heading:

- XARTEMIS XR is intended for oral use only. Abuse of XARTEMIS XR poses a risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing, or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk of overdose and death is increased with concurrent abuse of alcohol or other central nervous system depressants
- With intravenous abuse, the inactive ingredients in Xartemis XR can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

Clinical Studies

The Clinical Studies Section 14 was revised from the Applicant's original wording to read as follows:

Post-Operative Bunionectomy Pain Study

Efficacy was demonstrated in one multicenter, randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose clinical trial comparing XARTEMIS XR and placebo in patients with acute pain following a unilateral first metatarsal bunionectomy. A total of 303 patients with a mean age of 43 (range 18 to 73) years, meeting criteria for **randomization (pain intensity ≥4 on a 0 to 10 numerical pain** rating scale) and receiving a fixed-dose of 2 tablets of XARTEMIS XR, 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen tablets or placebo every 12 hours over 48 hours were randomized. There were 36 early discontinuations (9% from XARTEMIS XR, 13% from placebo). Ibuprofen 400 mg every 4 hours as needed was allowed as rescue medication.

Mean baseline pain intensity scores were 6.2 in the XARTEMIS XR group (range: 4 to 10) and 6.0 in the placebo group (range: 1 to 10. Approximately 85% of the 150 subjects treated with XARTEMIS XR and 98% of the 153 subjects treated with placebo took rescue medication at least once for pain management during the 48 hours after the first dose. Median rescue medication use was 2 doses for XARTEMIS XR-treated subjects and 4 doses for placebo-treated subjects over the 48 hours; rescue medication was used by less than 50% of the XARTEMIS XR-treated patients after the first dose interval. Pain intensity was recorded at 2, 4, 8, and 12 hours after each dose, with additional recordings at 15, 30, 45, 60, and 90 minutes after the first dose. The median time to onset of pain relief was less than one hour for XARTEMIS XR. The primary endpoint was the summed pain intensity difference (change in pain from baseline) over 48 hours ($SPID_{48}$), which demonstrated improvement in pain from baseline for the XARTEMIS XR treatment group compared to placebo.

8. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  Approval

- Risk Benefit Assessment

Refer to my original CDTL memo for discussion or the risk benefit assessment in terms of efficacy and safety. With regard to the inclusion of abuse deterrent language in the label, I agree with CSS that the Applicant has failed to adequately demonstrate AD properties that warrant inclusion of the findings in the label.

Approval of Xartemis XR will result in the entrance into the marketplace of an extended-release opioid that is not abuse deterrent. However, the following attributes of this product make its risks more similar to the immediate-release oxycodone/APAP combination than to extended-release opioid analgesic products:

- The low dose of oxycodone (7.5 mg) per tablet which is the same as in the immediate-release oxycodone/APAP combination product
- The major difference between Xartemis XR and Percocet is the dosing interval (Q 12 hours vs Q 4-6 hours)
- The formulation includes both ER and IR components of oxycodone
- The product is combined with a non-opioid (APAP), so that the labeled dose is limited to mitigate the risk of hepatotoxicity

Therefore, although Xartemis XR has extended-release properties, its absence of meaningful AD does not preclude its approval.

As previously noted in my original CDTL memo and by DRISK (below) in their memo dated January 28, 2014, risk mitigation measures beyond professional labeling and a Medication Guide are not warranted.

> The safety profile for Xartemis XR is consistent with currently approved IR formulations of oxycodone/acetaminophen. There were no new or unique safety concerns associated with Xartemis XR identified in the pivotal trials. Furthermore, the IR oxycodone/acetaminophen combinations do not currently have an approved REMS. Therefore, a REMS is not recommended for Xartemis XR.

The Division agrees that product labeling, a Medication Guide, and routine pharmacovigilance appear adequate to mitigate the risks of this product.

- Recommendation for other Postmarketing Requirements and Commitments

See prior CDTL memo

- Recommended Comments to Applicant

None

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

/s/

ELLEN W FIELDS
02/24/2014

Cross-Discipline Team Leader Review

Date	November 7, 2013
From	Ellen Fields, MD, MPH Clinical Team Leader, DAAAP
Subject	Cross-Discipline Team Leader Review
NDA#	204031
Applicant	Mallinckrodt, Inc.
Date of Submission	May 28, 2013
PDUFA Goal Date	November 28, 2013
Proprietary Name / Established (USAN) names	Xartemis XR/ oxycodone HCl and acetaminophen
Dosage forms / Strength	7.5mg oxycodone + 325mg acetaminophen extended-release tablets
Proposed Indication(s)	Management of (b) (4) acute pain where the use of an opioid analgesic is appropriate
Recommended:	Approval

1. Introduction

NDA 204031 was submitted by Mallinckrodt Inc. (the Applicant) as a 505(b)(2) application for COV795 (oxycodone hydrochloride and acetaminophen) extended-release tablets for the management of (b) (4) acute pain. The Applicant states that this product was formulated with physiochemical characteristics intended to deter abuse. This application relies in part on the Agency's previous findings of safety and efficacy for two Listed Drugs, Roxicodone (NDA 21011, Mallinckrodt, oxycodone 15mg tablets) and Ultracet (NDA 21123, Janssen, tramadol 37.5mg/acetaminophen 325mg). COV795 will be referred to as Xartemis XR, the approved proprietary name, throughout this review.

This review will summarize the findings of the review disciplines including the Controlled Substance Staff (CSS) review of the studies related to the in vitro and in vivo abuse-deterrent properties of Xartemis XR. Discussions regarding the applicability of the extended-release/long acting (ER/LA) REMS to this product and the approvability of this extended-release opioid in the absence of abuse-deterrent labeling language will also be included in this review.

2. Background

Xartemis XR is a fixed-dose, opioid/non-opioid combination that includes both immediate-release (IR) and controlled-release components of oxycodone (OC) and APAP. The product incorporates Depomed's AcuForm™ gastroretentive (GR) drug delivery technology. This is intended to allow release of the active pharmaceutical ingredients into the upper gastrointestinal tract (UGI) over an extended period of time. The Applicant also proposes that

the GR delivery system conveys potential tamper and abuse-deterrent properties to the product.

Xartemis XR tablets (7.5 mg OC/325 mg APAP) contain (b) (4) in the IR layer component designed to provide early onset of analgesia. The ER layer component contains (b) (4) to provide an extended duration of analgesia when administered orally every 12 hours (Q12h). Xartemis XR is intended for administration as 2 tablets Q12h (30 mg OC/1,300 mg APAP total daily dose).

This product is unique in that it is the first extended-release oxycodone/APAP combination product. This combination has been approved and marketed as an immediate-release product for decades as oral capsules, tablets and solution, containing up to 10 mg of oxycodone and 500 mg of APAP per unit, for the management of acute pain.

Xartemis XR is also unique in that it is the only extended-release opioid/non opioid combination, and the only extended-release opioid intended for the management of acute pain. All other extended-release opioids are indicated for the management of chronic pain.

During development of Xartemis XR, the Division conveyed to the Applicant that due to its ER properties, if approved, Xartemis XR would become part of the class-wide extended-release/long-acting (ER/LA) opioid Risk Evaluation and Mitigation Strategy (REMS), despite the difference in indication between the other ER/LA opioid products and Xartemis XR. However, during review of the application, the Division has determined, for reasons discussed in detail later in this review that Xartemis XR should not, in fact, become part of this REMS.

The Applicant has submitted the results of in vitro and in vivo abuse liability studies in order to demonstrate Xartemis XR's abuse-deterrent properties. CSS has conducted an in depth review of these studies which will be discussed in this review. According to the January, 2013, *Draft Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling*, "When the data predict or show that a product's potentially abuse-deterrent properties can be expected to, or actually do, result in a significant reduction in that product's abuse potential, these data, together with an accurate characterization of what the data mean, should be included in product labeling… It is critical that labeling claims regarding abuse-deterrent properties be based on robust, compelling, and accurate data and analysis, and that any characterization of a product's abuse-deterrent properties or potential to reduce abuse be clearly and fairly communicated." CSS has determined that the results of the studies submitted by the Applicant do not meet the standards for labeling described in the guidance.

3. CMC/Device

The CMC review was conducted by Yong Hu, Ph.D. with secondary concurrence by Prasad Peri, Ph.D. From the CMC perspective there were no issues that preclude approval of this NDA. The following is a summary of key findings from the CMC review.

Drug Product

The drug product is a bilayer ER tablet, comprised of an IR and an ER layer. The tablet contains 7.5 mg oxycodone HCl and 325 mg APAP. The IR layer contains (b) (4) of the total

oxycodone and (b) (4) of the total APAP dose. The ER layer contains (b) (4) respectively of the active ingredient dose. It is manufactured at (b) (4) in (b) (4).

The product is a modified oval-shaped blue tablet with a debossed logo of an "M" in a box over "115" on the IR side of the tablet. The biopharmaceutics reviewer determined that the debossing does not affect tablet dissolution.

There are two container closure systems proposed for the commercial product, HDPE 100 count bottles and blister packs (b) (4)

Drug Substance

The drug substance information is provided in DMF 5326 (APAP) and DMF 6930 (oxycodone HCl), both of which have previously been deemed adequate to support ANDAs. Oxycodone and APAP drug substances are manufactured by Mallinckrodt, Inc. in St. Louis, Missouri and in Raleigh, North Carolina, respectively. The oxycodone HCl drug substance has a low level (up to (b) (4)%) of the impurity 14-hydroxycodeinone (USP related compound A), an (b) (4) (b) (4) According to an FDA General Advice Letter issued to the DMF holder, the (b) (4)% specification limit is acceptable for a maximum daily dose of (b) (4) of oxycodone HCl (b) (4)

Stability

The drug product stability data cover 12-month storage under the long-term (25ºC/60% RH) and intermediate (30ºC/65%RH) conditions and 6-month storage under the accelerated (40ºC/75%RH) condition.

Facilities review/inspection

The Office of Compliance has deemed all the manufacturing and testing facilities for the drug substances and drug product acceptable in the Establishment Evaluation System (EES).

The CMC team has not recommended any postmarketing commitments.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Elizabeth Bolan, Ph.D., with secondary concurrence by Daniel Mellon Ph.D. From the pharmacology/toxicology perspective there were no issues that preclude approval of this NDA. The following is a summary of key findings from Dr. Bolan's review.

As stated on page 6 of Dr. Bolan's review:

> The Applicant is submitting NDA 204031 via the 505(b)(2) regulatory pathway with Roxicodone (NDA 21011) and Ultracet (NDA 21123) as the referenced products. The Applicant is relying on the Agency's findings of

safety and the relevant pharmacology, pharmacokinetics, and toxicology information in the labels of the referenced products and on published literature. No new nonclinical studies with oxycodone or acetaminophen or the combination were required for this NDA. The excipients in the formulation can be found in higher amounts in approved chronic use drug products and do not pose any novel toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. There are no unique nonclinical issues with this product as compared to other oral formulations of its individual components, oxycodone and acetaminophen

The review team has recommended changes to the Applicant's proposed label, Section 8 USE IN SPECIFIC POPULATIONS in order to provide an updated risk summary for use in pregnancy. Changes were also recommended for Section 13 NONCLINICAL TOXICOLOGY to update information on carcinogenesis, mutagenesis, and impairment of fertility. These changes have been incorporated into the label.

No postmarketing commitments were recommended.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Wei Qiu, Ph.D., with secondary concurrence by Yun Xu, Ph.D. From the clinical pharmacology perspective there were no issues that preclude approval of this NDA. The following is a summary of key findings from Dr. Qiu's review.

The clinical pharmacology database for this NDA consisted of 11 pharmacokinetic (PK) studies. Dr. Qiu's review focused on studies that utilized the final to-be-marketed debossed tablet, that included two relative bioavailability studies (Studies 256 and 255), a food effect study (Study 171), and a human abuse liability (HAL) study (Study 244). The formulation utilized in the HAL study was identical to the final-to-be marketed formulation except the tablets were not debossed. The debossed and non-debossed tablets were linked using comparative hardness and dissolution data, which was acceptable to the Biopharmaceutics team.

As there is not an approved NDA product that contains oxycodone and APAP in combination, the Division (b) (4) (b) (4) did agree with the Applicant's alternate proposal to rely on Roxicodone and Ultracet, as noted earlier in this review.

As stated on pages 3- 5 of Dr. Qiu's review:

Relative Bioavailability of Xartemis in Comparison to the Listed Drugs ((Roxicodone tablet and Ultracet tablet)

Single Dose:

After dose normalization, Xartemis exhibited equivalent systemic exposure to oxycodone in comparison to listed drug, Roxicodone tablet. The point estimate (90% CI) of the geometric mean ratio (Xartemis tablets/Roxicodone tablet) for dose normalized Cmax, AUCt, and AUCinf values of oxycodone are 92% (85 – 100%), 100% (96 – 105%), and

100% (96 – 105%), respectively. After dose normalization, Xartemis has equivalent systemic exposure to acetaminophen in comparison to listed drug, Ultracet tablet. The point estimates (90% CI) of the geometric mean ratios (Xartemis tablet/Ultracet tablet) for dose normalized Cmax, AUCt and AUCinf values of acetaminophen are 106% (98 – 115%), 96% (94 – 99%), and 98% (96 – 101%), respectively.

Multiple Doses:

After dose normalization, Xartemis exhibited equivalent systemic exposure to oxycodone in comparison to listed drug, Roxicodone tablet. The point estimate (90% CI) of the geometric mean ratio (Xartemis tablets/Roxicodone tablet) for dose normalized Cmaxss and AUC0-12ss are 107% (98 – 117%) and 110% (104 – 117%), respectively. After dose normalization, Xartemis has equivalent Cmax and AUC values to acetaminophen in comparison to listed drug, Ultracet tablet. The point estimates (90% CI) of the geometric mean ratios (Xartemis tablet/Ultracet tablet) for dose normalized Cmaxss and AUC0-12ss values of acetaminophen are 96% (85 – 107%) and 95% (91 – 99%), respectively.

acetaminophen. Low fat and high fat meals decreased acetaminophen Cmax values by 23 to 24%. These changes in Cmax and AUC values of oxycodone and acetaminophen are considered to be not significant and the product can be taken without regard to meals.

Alcohol Effect:

Refer to the ONDQA/Biopharm review for the In vitro alcohol effect on the dissolution of Xartemis. Per Pre-NDA meeting minutes, it was agreed that the results of dissolution testing do not indicate potential for dose-dumping in the presence of alcohol, and that an in vivo human alcohol interaction study will not be necessary. Sponsor did not conduct in vivo alcohol interaction study for Xartemis.

Multiple Dose PK of Xartemis:

After multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were achieved following 1 day administration since the pre-dose concentration obtained on Days 2 through 5 were similar. The accumulation index calculated as the Cmin under steady state conditions divided by the Cmin after the first dose, drug accumulates 1.7 fold for oxycodone and 1.4 fold for acetaminophen.

Food Effect:

Low and high fat meals delayed median oxycodone Tmax by 1 and 2 hrs, respectively. On average, low fat and high fat meal increased AUCt and AUCinf by 15% but the 90% CIs for the geometric mean ratios (low fat fed/fasting or high fat fed/fasting) were within the no effect range of 80% to 125%. Low fat meal increased oxycodone Cmax by 25% and high fat increased oxycodone Cmax by 12%. The 90% CIs for the geometric mean ratios of Cmax values are 117 to 134% and 105 to 102%, for low fat fed/fasting and high fat fed/fasting, respectively. Low and high fat meals delayed median acetaminophen Tmax by 1.5 hours. Either low fat or high fat meal did not affect the AUC values of

Dr. Qiu also reviewed the PK data from the HAL study. This study compared the likeability and PK of overencapsulated crushed and intact Xartemis XR. (b) (4)

(b) (4)

(b) (4)

Details are discussed later in this review.

In summary, the key findings from the clinical pharmacology review are:

1. Xartemis exhibited equivalent dose normalized Cmax and AUC values of oxycodone and acetaminophen in comparison to the respective listed drugs, Roxicodone (oxycodone HCl) and Ultracet (tramadol HCl/acetaminophen) tablets following both single dose and multiple dose administrations.
2. Both low fat and high fat foods do not have a significant effect on oxycodone and acetaminophen pharmacokinetics following the single dose administration of Xartemis; the product can be taken without regard to meals.
3. After multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were achieved following 1 day administration.

Sandra Suarez Sharp, Ph.D., conducted the biopharmaceutics review with secondary concurrence by Angelica Dorantes, Ph.D., and Richard Lostritto, Ph.D. They did not identify any issues that would preclude approval of this NDA. The biopharmaceutics review focused on the acceptability of the dissolution method and acceptance criteria, the extended-release designation claim, and the in vitro in vivo relationship (IVIVR) supporting the clinical relevance of the dissolution method, the in vitro alcohol dose-dumping studies, the use of dissolution to support "in process" and proposed drug product specifications and the debossing manufacturing change. The following are Dr. Sharp's conclusions:

- The dissolution method and acceptance criteria agreed upon with the Applicant are acceptable.
- The Applicant was informed during the review cycle that the proposed IVIVR is not acceptable (b) (4)
- Based on the PK performance with acceptable and consistent variability among subjects, the absence of dose-dumping in the presence of food, the prolonged Tmax in relation to the listed drugs, and similar degree of fluctuation and swing compared to the selected listed drugs, the proposed product meets the requirements for an extended-release designation claim.
- There were no signs of in vitro dose dumping in the presence of alcohol when tested in the QC media and in phosphate buffer pH 6.8. The dissolution rate was decreased in the presence of 40% alcohol for both OC and APAP.
- The drug product appears to meet the recommended dissolution acceptance criteria and the proposed viscosity specification limits are acceptable.

6. Clinical Microbiology

A clinical microbiology review was not necessary for this application as Xartemis XR is not an antimicrobial.

7. Clinical/Statistical- Efficacy

The efficacy review was conducted by Elizabeth Kilgore, MD, and the statistical review was conducted by Feng Li, Ph.D., with concurrence from Janice Derr, Ph.D. There were no issues noted by either discipline that would preclude approval of this NDA.

The Xartemis XR clinical development program included 12 Phase 1 studies and two Phase 3 (one adequate and well-controlled (AWC) and one open-label study) studies and was designed to support an indication of the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate

In light of the fact that there are decades of experience with approved analgesic combination products containing oxycodone and APAP, at the End-of-Phase 1 meeting held in December, 2011, the Division agreed to the submission of a single a single, adequate and well-controlled efficacy study to support efficacy for the proposed indication, management of (b) (4) (b) (4) acute pain where the use of an opioid analgesic is appropriate. Typically, a factorial design study would be required for a combination product in which both components contribute to the analgesic efficacy of the product, however, as this product includes a well-known analgesic combination, a factorial study was not necessary. The Phase 3 efficacy study, Study 0182, was a randomized, double-blind, placebo-controlled efficacy study in 329 subjects with postoperative bunionectomy pain. The Division agreed that this pain model would be generalizable to the target population of patients with acute pain.

Drs. Kilgore and Li reviewed Study 0182 in depth, and what follows is a summary of the key efficacy findings from their reviews.

Study 0182 was titled, A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Evaluation of the Safety and Analgesic Efficacy of COV795 (Oxycodone HCL/Acetaminophen) ER Tablets in Moderate-to-Severe Post-Operative Bunionectomy Pain followed by an Open-Label Extension. The study enrolled 329 subjects at five sites, and included a 48-hour double-blinded dosing phase followed by an optional 14-day open-label extension. The double-blind portion of the study was intended to assess efficacy and safety, and the open-label portion to provide additional safety data. Study subjects with acute postoperative pain of moderate-severe intensity (a score of at least 4 on an 11-point numerical rating scale, following unilateral bunionectomy surgery were randomized equally to receive either Xartemis XR (2 tablets OC 7.5mg/APAP 325 mg) or placebo. Rescue medication (ibuprofen 400mg) was provided and could be taken as needed up to six times per day. Pain intensity was recorded at 2, 4, 8, and 12 hours after each dose, with additional measurements at 15, 30, 45, 60, and 90 minutes after the first dose.

In the original iteration of the protocol, subjects were given an initial dose of Xartemis XR, and could request a second dose when they determined it was needed. Following the second

dose, the dosing in the study continued every 12 hours. Amendment 2 modified the protocol so that all subjects received fixed every 12 hour dosing. Twenty-six subjects were enrolled prior to Amendment 2, and were designated as Cohort 1. The remaining 303 subjects enrolled after Amendment 2 were designated as Cohort 2.

The primary efficacy variable was the summed pain intensity difference over the first 48 hours (SPID48) in subjects with moderate-to-severe acute pain following unilateral bunionectomy. The pain intensity difference (PID) was defined as the baseline pain intensity score minus the pain intensity score at the time point of interest. The secondary efficacy endpoints included pain relief, time to onset of relief (double-stopwatch method), use of rescue medication, and subject's global assessment.

Results

The subject disposition is below as stated in Dr. Li's review on p. 10:

A total of 329 subjects were randomized from five sites, 164 to COV795 and 165 to placebo. There were 26 subjects in Cohort 1 and 303 subjects in Cohort 2. The 303 subjects in Cohort 2 constituted the mITT population, the primary efficacy population. Overall, approximately 11% of the subjects discontinued early (Table 1). The dropout rates of the COV795 and placebo groups were 10% and 12% respectively. The most common reasons for early discontinuation were lack of efficacy and adverse events. Of the 22 subjects in the mITT population that discontinued because of lack of efficacy, seven subjects (5%) were taking COV795 and 15 subjects (10%) were taking placebo. There were seven subjects (5%) from the COV795 group and two subjects (1%) from the placebo group who discontinued because of adverse events. The disposition including subjects from both Cohort 1 and Cohort 2 was similar.

The demographic and baseline characteristics were similar between the two treatment groups (Table 2). The majority of subjects were female (85%) and mean subject age was 43 years. Overall, 59% of subjects were white.

Table 1: Subject Disposition – Number (%) of Patients

	COV795	Placebo	Total
Modified Intention-to-treat (mITT)	**150**	**153**	**303**
Discontinuation during blinded dosing period	15 (10%)	19 (12%)	34 (11%)
Lack of efficacy	7 (5%)	15 (10%)	22 (7%)
Adverse event	7 (5%)	2 (1%)	9 (3%)
Withdrawal by subject	1 (1%)	2 (1%)	3 (1%)

Source: Clinical study report, Table 14.1-1 and Table 14.1-3

Dr. Li was able to replicate the Applicant's results for the primary efficacy analysis as shown below. Xartemis XR was superior to placebo in terms of SPID 48 with statistical significance. According to Dr. Li, if divided by 48, the duration in hours, the treatment difference of 48 translates to a treatment effect of 1 point on the 11-point NRS in terms of average pain reduction from baseline over 48 hours. According to Dr. Li, the inclusion of only Cohort 2 in the primary efficacy analysis is acceptable. He conducted a sensitivity analysis including all randomized subjects from both Cohorts 1 and 2, and the results were similar.

Table 3: Primary Efficacy Analysis Results (SPID48)

Method	Statistics	COV795 (N=150)	Placebo (N=153)	95% CI	P-value
Multiple imputation (50 imputations)	Mean (SE)	115 (7)	67 (7)		
(pain scores 6 hours after rescue censored)	Difference (SE)	48 (11)		(27, 69)	<0.001

Source: Clinical Study Report, Table 14.2-2.1; SE: standard error; CI: confidence interval

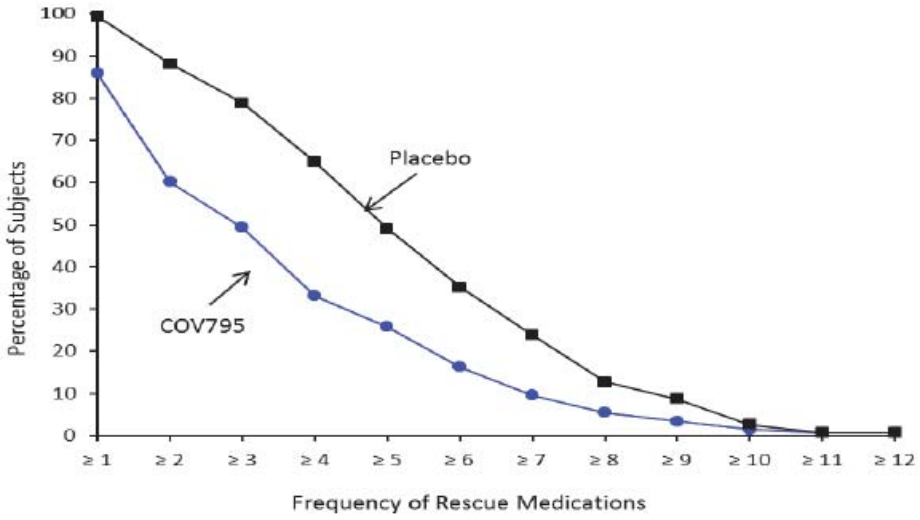
As stated in Dr. Li's review on page 8:

The primary analysis was based on an analysis of covariance model (ANCOVA) with terms including treatment, baseline pain score, site, and treatment-by-site interaction. The applicant defined the primary efficacy population as the modified intent-to-treat (mITT) population, which included all randomized subjects from Cohort 2. As for the rationale to exclude those subjects in Cohort 1, the applicant stated that it was difficult to align the pain assessments between the two cohorts.

Any pain intensity score that was not collected because a subject withdrew before the 48-hour blinded dosing period was considered as missing. The pre-rescue pain score was used to replace the next scheduled pain assessment within 6 hours of receiving rescue. Any other scheduled pain assessments that occurred within 6 hours following rescue were considered as censored (missing) in the analyses.

A very high percentage of subjects took rescue analgesic medication during the 48 hours double-blind period, approximately 85% of the Xartemis XR treatment group and 99% of the placebo group. Subjects in the placebo group took rescue more often than the Xartemis XR group as shown in the following figure from page 12 of Dr. Li's review.

Figure 1: Percentage of Subjects with Different Frequency of Rescue Use

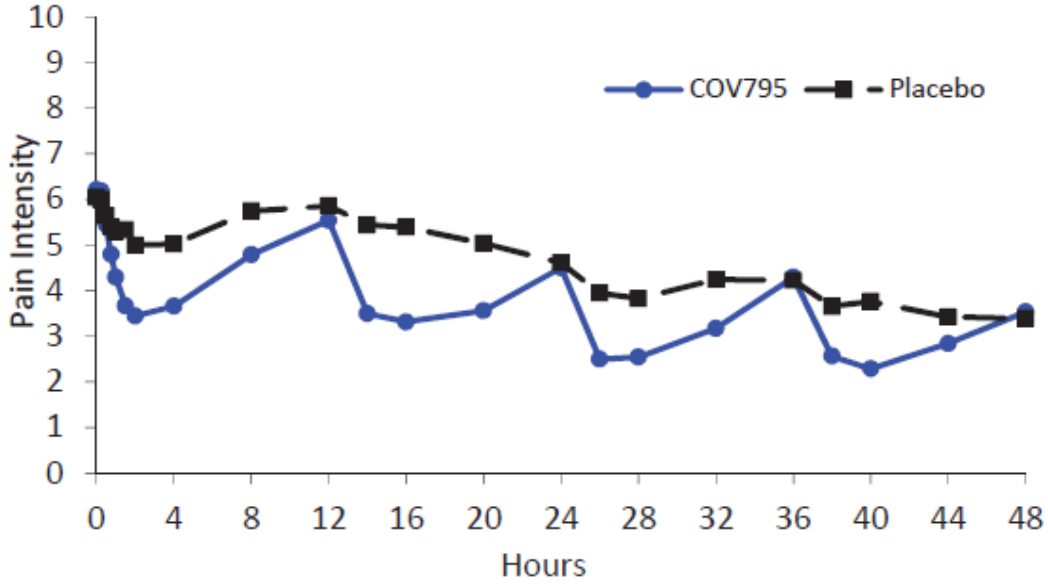


Dr. Li had concerns regarding the strategy used by the Applicant to handle pain scores following rescue use. The pre-rescue pain score was used to replace the next scheduled pain

assessment within 6 hours of receiving rescue. Any other scheduled pain assessments that occurred within 6 hours following rescue were considered missing in the analysis. This approach created a large number of intermittent missing values. These intermittent missing values were subsequently imputed using a MCMC approach that assumes that subjects who took rescue were all alike and the other subjects were all alike. Dr. Li conducted a number of sensitivity analyses for the primary endpoint with differing approaches to incorporating pain scores obtained before and after rescue medication use, and all confirmed the prespecified primary efficacy results and allayed his concerns.

In terms of secondary analyses, pain intensity over time by treatment group results in the following curve from page 14 of Dr. Li's review. According to these results, the decrease in pain intensity in the Xartemis XR group approaches that of placebo at approximately 12 hours for each of the 4 doses in the double-blind period.

Figure 2: Average Pain Intensity Over Time – Including Pain Intensities After Rescue



Rescue Use and Dosing Interval

In the double-blind study, a smaller proportion of subjects in the Xartemis XR group compared to placebo used rescue medication after the first dose, subsequent doses and overall during the 48-hour double-blind period, however, the rates of rescue use in both groups were very high. Eighty-five percent of subjects in the Xartemis XR group used at least one dose of rescue compared to 99% in the placebo group. In the first 12 hours after the first dose, 80% of Xartemis XR subjects used rescue compared to 96% of placebo subjects. The proportion of subjects in both groups using rescue decreased for subsequent doses. These findings are detailed in the following table:

Table 11.4.1.3.7-7: Percentage of Subjects Using Rescue Medication (mITT Population)

Subject Used Rescue Medication During Dosing Interval Category	COV795 (N = 150)[a] n (%)	Placebo (N = 153)[a] n (%)	*P* Value[b]
Subject Used at Least One Dose of Rescue Medication[c]			< 0.0001
Yes	127 (85.8)	150 (99.3)	
No	21 (14.2)	1 (0.7)	
Between Doses 1 to 2			< 0.0001
Yes	118 (79.7)	146 (96.7)	
No	30 (20.3)	5 (3.3)	
Between Doses 2 to 3			< 0.0001
Yes	69 (48.9)	119 (83.8)	
No	72 (51.1)	23 (16.2)	
Between Doses 3 to 4			< 0.0001
Yes	62 (45.9)	102 (75.6)	
No	73 (54.1)	33 (24.4)	
Between Dose 4 to End of Period			0.0006
Yes	53 (39.3)	79 (59.0)	
No	82 (60.7)	55 (41.0)	

Source: Table 14.2-13.1
Source: Study report 0182, p. 91

The time to use of first rescue medication is shown below. The Applicant states that the short duration of analgesia after the first dose of study medication is classically observed with the bunionectomy pain model, because these patients have more severe pain immediately after surgery, and that the average baseline pain for patients in this study was 6 on the NPRS, higher than the score of 4 that was required for inclusion into the study. However for subsequent doses, the median time to rescue medication (e.g., dosing interval) was 12 hours, and the mean time ranged from 8.6 to 9.6 hours, with the duration between doses increasing with time.

Table 11.4.1.3.7-9: Rescue Intervals (mITT Population)

Dosing Interval (Hours)[a]	COV795 (N = 150)[b] n (%)	Placebo (N = 153)[b] n (%)	*P* value[c]
Between 0 and 12 hour Doses			
N	148	151	< 0.0001
Mean (SD)	6.19 (3.92)	3.35 (2.76)	
Median	5.75	2.15	
Q1, Q3	2.2, 9.8	1.4, 4.2	
Minimum, Maximum	1.1, 12.1	1.1, 12.0	
Between 12 and 24 hour Doses			
N	141	142	< 0.0001
Mean (SD)	8.61 (4.03)	4.81 (3.89)	
Median	12.0	2.99	
Q1, Q3	4.5, 12.0	1.8, 8.1	
Minimum, Maximum	0.8, 12.1	1.0, 12.1	
Between 24 and 36 hour Doses			
N	135	135	< 0.0001
Mean (SD)	9.43 (3.39)	6.29 (3.93)	
Median	12.0	5.12	
Q1, Q3	7.2, 12.0	2.7, 10.5	
Minimum, Maximum	0.5, 12.1	0.3, 12.1	
Between 36 and 48 hour Doses			
N	135	134	< 0.0001
Mean (SD)	9.61 (3.78)	7.27 (4.52)	
Median	12.0	7.85	
Q1, Q3	8.1, 12.0	2.3, 12.0	
Minimum, Maximum	0.7, 12.0	0.8, 12.0	
Average Dosing interval[d]			
N	148	151	< 0.0001
Mean (SD)	8.21 (3.10)	5.18 (2.68)	
Median	8.88	4.83	
Q1, Q3	5.6, 10.9	2.8, 7.2	
Minimum, Maximum	1.1, 12.0	1.1, 12.0	

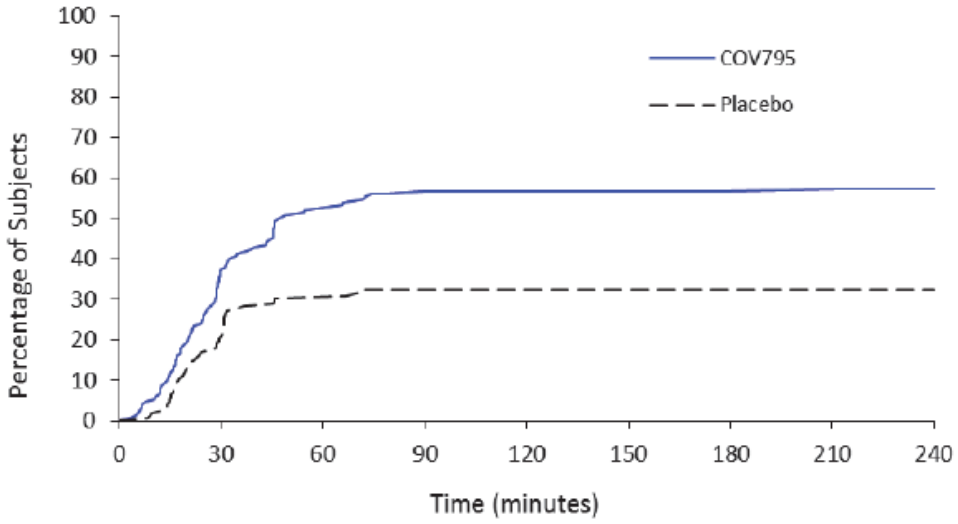
Source: Table 14.2-13.3
Q = quartile.
[a] Rescue interval was defined as the time from the dose of study drug to the first rescue medication use during the interval or the next dose, whichever came first. For the last interval, the rescue interval was the time from the last dose in the blinded dosing period to first rescue medication or 12 hours post-dose. Subjects who discontinued early and did not receive any rescue medication within a given interval were not included in that interval.
[b] Summary was by randomized treatment during the blinded dosing period. Subjects 201-120 and 204-098 were randomized to placebo, but actually received COV795.
[c] *P* value was based on a ranked ANOVA with treatment as the main effect.
[d] For each subject, overall dosing interval was taken as the mean of the nonmissing dosing intervals.

The Applicant intends for Xartemis XR to be administered every 12 hours, which given these results (rescue use and pain intensity over time), is not supported for the initial dose. While the Applicant may be correct that the study subjects' pain levels were too high to obtain pain relief for the full 12 hours after the first dose, they have not provided data that supports the notion that patients who receive Xartemis XR post approval will have 12 hours of pain relief. For subsequent doses, the median time to rescue/next dose was 12 hours, and the mean time was in the 8 to 9 hour range. Based on this data, an every 8 to 12 hour dosing interval following the initial dose appears more appropriate.

Approximately 50% of the subjects taking Xartemis XR (median time 48 minutes) and 30% of the subjects taking placebo experienced confirmed perceptible pain relief within one hour after the first dose (Figure 4 taken from Dr. Li's review).

Analyses of other secondary efficacy endpoints including the time to first rescue and patient's global impression were supportive to the primary analysis.

Figure 4: Time to Confirmed Perceptible Pain Relief



Subgroup analyses of the primary endpoint for gender, age, and race were consistent with those observed for the overall population.

I am in agreement with both Dr. Kilgore and Li's conclusions that efficacy was demonstrated for Xartemis XR in a single, adequate and well-controlled trial in patients with post bunionectomy pain. The high rescue use in the Xartemis XR treatment group indicates that the pain model used may not have been the best choice. Nonetheless, despite the high level of rescue use, the study drug was statistically significantly superior to placebo. The secondary endpoints supported the primary endpoint findings.

I disagree with the primary reviewer regarding the Applicant's proposed dosing interval. Although efficacy for Xartemis XR was established in the Phase 3 study that utilized an every 12 hour dosing interval, the data on rescue use and pain intensity over time compared to placebo does not support every 12 hour dosing for the initial dose of Xartemis XR. Despite the Applicant's justification that pain following surgery is very severe, a more appropriate dosing interval for Xartemis XR may be every 8-12 hours for the first dosing interval, rather than every 12 hours. This would allow patients requiring earlier analgesia to safely take a second dose. The total daily dose of APAP would remain well below the maximum of 4 gms, and the daily dose of oxycodone would still be within that achieved with IR oxycodone/APAP combination products.

8. Safety

The safety review was conducted by Dr. Kilgore. Overall there were no new or unexpected safety signals detected in review of the Applicant's data. The following summarizes Dr. Kilgore's key findings.

During the development program for Xartemis XR, 834 subjects were exposed to the to-be-marketed dosing regimen of two tablets every 12 hours. The Applicant included a number of pooled groups in the integrated summary of safety (ISS), the most useful being the pooled Phase 3 studies (Study 0181 and Study 0182-efficacy study). Study 0181 was an open-label multicenter Phase 3 study designed to collect safety data in patients with pain due to OA and chronic low back pain (CLBP). Refer to Dr. Kilgore's review for safety findings regarding the Phase 1 studies. There were no new or unexpected safety signals detected in these studies.

The following table from page 78 of Dr. Kilgore's review details the exposure to Xartemis XR in the Phase 3 studies. Approximately 600 subjects were exposed, 347 of whom were exposed for 10 days or more. The maximum duration of treatment with Xartemis XR in the Phase 3 studies was 42 days, and the mean duration was 20 days.

	COV795-15/650					
Study[a]	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
COV15000181	42 (24.4)	20 (22.7)	310 (89.3)	372 (61.3)	0	372 (53.1)
COV15000182	130 (75.6)	68 (77.3)	37 (10.7)	235 (38.7)	163 (100)	329 (46.9)

Source: Section 23, Table 1.2.
Note: Percentages were calculated based on the number of subjects in the safety population in each treatment group.
[a]Subjects presented are more accurately referred to as exposures.

The extent of exposure from the Applicant's ISS is shown below:

Table 2.7.4.1.2-1: Extent of Exposure (Safety Population - Phase 3 Integration Set)

	COV795-15/650				
Statistic	< 5 days N = 172	5 to < 10 days N = 88	≥ 10 days N = 347	Overall N = 607	Placebo N = 163
n	172	88	347	607	163
Mean	2.4	6.8	32.7	20.3	2.8
SD	0.95	1.40	7.79	15.50	0.62
Median	3.0	7.0	36.0	17.0	3.0
Minimum	1	5	10	1	1
Maximum	4	9	42	42	3

Source: NDA Section 5.3.5.3, ISS, Section 23, Table 4.2.
Note: Extent of exposure is defined as the total length of exposure in days (time from first dose of study drug to the last dose of study drug).

Demographically, the age range of the integrated Phase 3 study population exposed to Xartemis XR was 18 to 87 years, with a mean age of 50 years. Approximately 10% of the subjects were older than 65 years. Sixty-eight percent of the exposed subjects were female, and 63% were white.

Because this combination of drugs has been marketed for decades and safety concerns are generally well known, the exposure is adequate to determine the safety profile of Xartemis XR for the intended indication.

There were no deaths in the Phase 1 studies, and two deaths in the open-label Phase 3 study. Both deaths appear unlikely related to study drug. One was due to cardiorespiratory arrest in a

71 year old male with OA of the knee and a history of hypercholesterolemia and hypertension, both requiring medication. The second death was due to a motor vehicle accident in a 76 year old male with OA (last known dose of study medication was four days prior to accident).

There were a total of six non-fatal SAEs in the Phase 3 Integrated Set (five in study drug-treated and one in placebo-treated). Dr. Kilgore reviewed the SAEs in detail and determined that one may have been related to study drug administration. The SAE was abdominal pain requiring hospitalization in a 73 year old woman with chronic low back pain and a history of cervical cancer for which she received radiation. Following her first dose of a single tablet of Xartemis XR she experienced nausea, vomiting, dizziness, and abdominal pain. She was hospitalized and diagnosed with a large intestine ulcer and radiation colitis. The Sponsor stated that the drug was associated with the abdominal pain, which is possible, however the subject also had an abnormal GI tract unrelated to the study drug which may have caused the event.

The Applicant determined that a second SAE was also causally related to Xartemis XR, and I am in agreement with the Applicant. The event occurred in a 52 year old female who vomited after receiving her third dose of study drug. The following day she developed chest pressure and burning, and was admitted to the hospital and diagnosed with GERD. The event resolved the same day. Dr. Kilgore stated in her review that GERD implies an ongoing chronic condition, which is true, however it is likely that the study drug had some part in causing the patient's symptoms.

The remaining three non-fatal SAEs in patients who received Xartemis XR included deep vein thrombosis, atrial fibrillation, and pregnancy, none of which appear to have been causally related to study drug.

One subject who received placebo had an SAE of hypersensitivity on Day 1 of dosing. Symptoms included complaint of numbness all over body, shortness of breath, mild nausea, and palpitations. She was taken to the ER and treated with morphine IV and aspirin 81mg, presumably while an MI was ruled out. While in the ER a mild urticarial rash on the patient's left arm was observed, and she was diagnosed with an allergic reaction. It is unclear whether this was truly a case of hypersensitivity or an anxiety event. Although the patient was receiving placebo, the excipients in the placebo tablets were the same as the study drug, and therefore this event (hypersensitivity) should be included in the adverse event section of the label.

In the pooled Phase 3 studies 12.4% of subjects (14.2% Xartemis XR, 0.6% placebo) experienced at least 1 AE that led to discontinuation. The proportion of subjects that discontinued due to an AE decreased with increasing length of Xartemis XR exposure (32.6% < 5 days, 20.5% 5 to < 10 days, and 3.5% ≥ 10 days). This finding is consistent with development of tolerance to adverse reactions related to opioids with increasing duration of exposure. Vomiting and nausea were the most common AEs leading to discontinuation, as would be expected for an opioid. Other common AEs leading to discontinuation occurring in two or more subjects in any treatment group included dizziness, hepatic enzyme increase,

somnolence, and chest discomfort. Adverse events related to hepatic toxicity will be discussed in additional detail later in this section.

Table 2.7.4.2.1.4-1: Adverse Events Leading to Discontinuation by MedDRA System Organ Class and Preferred Term (Safety Population - Phase 3 Integration Set)

	COV795-15/650					
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 AE leading to discontinuation	56 (32.6)	18 (20.5)	12 (3.5)	86 (14.2)	1 (0.6)*	87 (12.4)
Cardiac Disorders	1 (0.6)	0	1 (0.3)	2 (0.3)	1 (0.6)	3 (0.4)
Cardio-respiratory arrest	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Palpitations	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Tachycardia	0	0	0	0	1 (0.6)	1 (0.1)
Ear and Labyrinth Disorders	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Vertigo	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Gastrointestinal Disorders	43 (25.0)	8 (9.1)	4 (1.2)	55 (9.1)	0	55 (7.8)
Dyspepsia	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Nausea	18 (10.5)	5 (5.7)	2 (0.6)	25 (4.1)	0	25 (3.6)
Vomiting	25 (14.5)	2 (2.3)	2 (0.6)	29 (4.8)	0	29 (4.1)
General Disorders and Administration Site Conditions	3 (1.7)	0	0	3 (0.5)	0	3 (0.4)
Chest discomfort	2 (1.2)	0	0	2 (0.3)	0	2 (0.3)
Fatigue	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Injury, Poisoning and Procedural Complications	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Road traffic accident	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Investigations	0	1 (1.1)	5 (1.4)	6 (1.0)	0	6 (0.9)
Alanine aminotransferase increased	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Hepatic enzyme increased	0	1 (1.1)	3 (0.9)	4 (0.7)	0	4 (0.6)
Liver function test abnormal	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Nervous System Disorders	5 (2.9)	5 (5.7)	1 (0.3)	11 (1.8)	0	11 (1.6)
Cognitive disorder	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Dizziness	2 (1.2)	2 (2.3)	1 (0.3)	5 (0.8)	0	5 (0.7)
Headache	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Sedation	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Somnolence	1 (0.6)	2 (2.3)	0	3 (0.5)	0	3 (0.4)
Psychiatric Disorders	0	2 (2.3)	0	2 (0.3)	0	2 (0.3)
Confusional state	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Dysphoria	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Hypopnoea	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders	2 (1.2)	1 (1.1)	0	3 (0.5)	0	3 (0.4)
Pruritus	1 (0.6)	1 (1.1)	0	2 (0.3)	0	2 (0.3)
Rash	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Vascular Disorders	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Deep vein thrombosis	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)

Source: NDA Section 5.3.5.3, ISS, Section 23, Table 8.1.

Common adverse events

The Applicant defined common adverse events as treatment emergent adverse events (TEAEs) that were reported by at least 2% of subjects and occurred more frequently with Xartemis XR than placebo. The Applicant's table below shows the TEAEs that occurred in at least 1% of subjects from the double-blind portion of Study 0182, which gives a more complete picture of the safety profile. As would be expected, the most common TEAEs are related to the opioid component of the combination, and include the typical opioid related AEs of constipation, nausea, vomiting, dizziness, headache, and somnolence. Approximately 54% of subjects who received Xartemis XR reported at least one TEAE, compared to 21% in the placebo group.

Table X: Study 0182 All TEAEs Occurring in Greater Than 1% of Subjects by MedDRA System Organ Class and Preferred Term (Blinded Safety Population)

	n (%)		
System Organ Class/ Preferred Term	COV795 (N = 166)	Placebo (N = 163)	Total (N = 329)
Subjects who reported any TEAE	89 (53.6)	35 (21.5)	124 (37.7)
Gastrointestinal disorders	64 (38.6)	16 (9.8)	80 (24.3)
Constipation	7 (4.2)	5 (3.1)	12 (3.6)
Dry mouth	1 (0.6)	2 (1.2)	3 (0.9)
Nausea	51 (30.7)	9 (5.5)	60 (18.2)
Vomiting	15 (9.0)	0	15 (4.6)
General disorders and administration site conditions	6 (3.6)	1 (0.6)	7 (2.1)
Oedema peripheral	2 (1.2)	0	2 (0.6)
Injury, poisoning and procedural complications	2 (1.2)	0	2 (0.6)
Excoriation	2 (1.2)	0	2 (0.6)
Nervous system disorders	43 (25.9)	13 (8.0)	56 (17.0)
Dizziness	22 (13.3)	2 (1.2)	24 (7.3)
Headache	16 (9.6)	8 (4.9)	24 (7.3)
Hypoaesthesia	1 (0.6)	2 (1.2)	3 (0.9)
Somnolence	6 (3.6)	1 (0.6)	7 (2.1)
Renal and urinary disorders	2 (1.2)	0	2 (0.6)
Dysuria	2 (1.2)	0	2 (0.6)
Skin and subcutaneous tissue disorders	15 (9.0)	7 (4.3)	22 (6.7)
Blister	2 (1.2)	1 (0.6)	3 (0.9)
Erythema	2 (1.2)	0	2 (0.6)
Pruritus generalized	2 (1.2)	0	2 (0.6)
Rash	3 (1.8)	2 (1.2)	5 (1.5)
Vascular disorders	2 (1.2)	1 (0.6)	3 (0.9)
Hot flush	2 (1.2)	1 (0.6)	3 (0.9)

Source: Table 14.3.1-6.
N = number of subjects in specified treatment arm; n = number of subjects with data available.
Medical Dictionary of Regulatory Activities, version 14.1 coding applied. Summary is by actual treatment received during the blinded dosing period.

Source: Dr. Kilgore's review, p. 109

The common TEAEs in the pooled Phase 3 studies are similar to those described above. Of note, with increased duration of exposure, nausea, vomiting, and dizziness decreased, while the incidence of constipation increased. The incidences of other nervous system disorders and pruritus varied but no clear trend was noted. The majority of TEAEs were mild or moderate in severity. The severe TEAEs that occurred in more than one subject who received Xartemis XR include nausea, vomiting, constipation, headache, and pruritus.

Table 10.1.1.2-1: Most Common Treatment-Emergent Adverse Events (Incidence in Total Treatment Group at Least 2%) by MedDRA System Organ Class and Preferred Term (Safety Population - Phase 3 Integration Set)

	COV795-15/650					
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 TEAE	115 (66.9)	59 (67.0)	195 (56.2)	369 (60.8)	35 (21.5)	392 (55.9)
Gastrointestinal Disorders	90 (52.3)	39 (44.3)	102 (29.4)	231 (38.1)	16 (9.8)	243 (34.7)
Nausea	76 (44.2)	24 (27.3)	56 (16.1)	156 (25.7)	9 (5.5)	162 (23.1)
Vomiting	45 (26.2)	11 (12.5)	22 (6.3)	78 (12.9)	0	78 (11.1)
Constipation	6 (3.5)	9 (10.2)	43 (12.4)	58 (9.6)	5 (3.1)	63 (9.0)
Nervous System Disorders	53 (30.8)	32 (36.4)	81 (23.3)	166 (27.3)	13 (8.0)	175 (25.0)
Dizziness	28 (16.3)	14 (15.9)	37 (10.7)	79 (13.0)	2 (1.2)	81 (11.6)
Somnolence	12 (7.0)	9 (10.2)	34 (9.8)	55 (9.1)	1 (0.6)	56 (8.0)
Headache	14 (8.1)	12 (13.6)	15 (4.3)	41 (6.8)	8 (4.9)	48 (6.8)
Skin and Subcutaneous Tissue Disorders	19 (11.0)	9 (10.2)	34 (9.8)	62 (10.2)	7 (4.3)	68 (9.7)
Pruritus	9 (5.2)	3 (3.4)	22 (6.3)	34 (5.6)	3 (1.8)	37 (5.3)

Source: Section 23. Table 5.5.1.

Laboratory, Vital Sign, and ECG Evaluations

Clinical laboratory evaluations included hematology, serum chemistry, and urinalysis. There were no unusual or unexpected findings. Changes in liver transaminase levels are discussed below with adverse events of special interest.

Dr. Kilgore reviewed vital sign assessments and pulse oximetry. There were no unexpected findings. There were also no clinically important abnormalities in ECGs that developed during treatment with study drug.

Adverse events of special interest

The Applicant and Dr. Kilgore conducted analyses of adverse events of special interest for the Phase 3 pooled data set. These events include those that may be associated with the formulation (choking, GI obstruction), and the API's (serious events known to occur with oxycodone or APAP such as cardiac, respiratory, GI, nervous system, hepatotoxicity, and serious skin reactions). The following is a brief summary of Dr. Kilgore's findings and additional analyses I conducted.

Choking, obstruction of the airway, and GI obstruction are potential risks associated with the Xartemis XR formulation because it contains polyethylene oxide (PEO), which causes the tablet to swell and become sticky when wet. I conducted a search of the safety database and found one case report of dysphagia from Phase 1 Study 0045 in which a healthy volunteer reported difficulty swallowing following administration of two tablets of Xartemis XR. The event resolved without treatment. There were no reported cases of choking, airway obstruction, or gastrointestinal obstruction in subjects who received Xartemis XR; however this safety issue remains a concern post approval when the exposure to this formulation increases. Product labeling must include instructions to swallow the tablets with ample water, not to wet the tablets prior to administration, and cautions regarding prescribing Xartemis XR to patients with underlying GI conditions that would predispose them to obstruction.

The Applicant conducted a Hepatic Disorders SMQ due to the presence of APAP in the formulation and its known risk of hepatotoxicity. The Phase 3 pooled data included treatment emergent hepatic disorders consisting of liver function test abnormalities (AST, ALT, GGT, transaminases increased). These occurred in 2% (12 subjects) of Xartemis XR treated subjects and in no placebo treated subjects. All increases were transient and reduced to normal or near normal in all subjects. A treatment duration of more than five days was associated with an increase in reports. LFT abnormalities led to discontinuation in 6 subjects (1%), all in Xartemis XR group. The following Applicant's tables detail the reported events and discontinuations.

Table 2.7.4.2.1.5.7-1: Treatment-Emergent Adverse Events by MedDRA Preferred Term - Standardized MedDRA Query for Hepatic Disorders (Safety Population - Phase 3 Integration Set)

	COV795-15/650					
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 treatment-emergent hepatic disorder	1 (0.6)	2 (2.3)	9 (2.6)	12 (2.0)	0	12 (1.7)
Hepatic enzyme increased	0	2 (2.3)	4 (1.2)	6 (1.0)	0	6 (0.9)
Alanine aminotransferase increased	0	0	2 (0.6)	2 (0.3)	0	2 (0.3)
Liver function test abnormal	0	0	2 (0.6)	2 (0.3)	0	2 (0.3)
Aspartate aminotransferase increased	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Gamma-glutamyltransferase increased	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Transaminases increased	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)

Source: NDA Section 5.3.5.3, ISS, Section 23, Table 5.8.1.

The Applicant's table below shows 10 placebo subjects with elevated LFTs that were apparently not reported as adverse events, and therefore were not included in the table above.

Summary of Liver Function Test (LFT) Elevations and Early Terminations due to Elevated LFTs

	Phase 3			Phase 1	
	0182 (RCT)		0181 (OL)		
Total Number of Subjects	MNK795	Placebo	MNK795	MNK795, Percocet, and Ultracet	Total
LFT 2.0 – 2.9 x ULN	4[a]	5[a]	13	1	23[a]
LFT 3.0 – 4.9 × ULN	2	4	6	-	12
LFT 5.0 – 9.9 × ULN	-	1[b]	4	1	6[b]
LFT ≥ 10 × ULN	2[b]	-	1	-	3[b]
Total bilirubin ≥ 2 × ULN	-	-	-	-	-
ET due to elevated LFTs	1	-	5	-	6

Note: Liver function test (LFT) values included: ALT, ALP, AST, direct bilirubin, GGT, LDH, total bilirubin; subjects are presented in the table with the greatest LFT value observed on study for any subject having an LFT ≥2 x ULN; - = '0' or no value
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ET = Early Termination (Discontinuation); GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; LFT = liver function test; OL = open label; RCT = randomized controlled trial; ULN = upper limit of normal.
[a]Subject 201-121 had LFT elevations in the Placebo treatment period (GGT), followed by elevations in the MNK795 treatment period- (GGT).
[b]Subject 202-047 had LFT elevations in the Placebo treatment period (ALT), followed by elevations in the MNK795 treatment periods (GGT).

Both of the subjects in Study 0182 who received Xartemis XR and had LFTs ≥ 10 X ULN had normal bilirubin levels throughout the course of the study. Subject 202-047, a 45 year old female had mildly elevated GGT (1.3 X ULN) and AST (1.4 X ULN) at baseline. Elevations of GGT, ALT, and AST (2.5 X ULN, 5.4 X ULN, and 3.3 X ULN respectively) occurred during treatment with placebo in the double-blind period, followed by worsening elevation of GGT (10X ULN), ALT (6.5 X ULN), and AST (7.5 X ULN) on Day 5 of the open-label extension treatment with Xartemis XR. Treatment was discontinued on Day 5, and all LFT's other than GGT (3.3 X ULN) returned to normal by Day 21. Because of the initial rise in LFTs during the placebo treatment, it is likely that these increases were due to a factor other than study drug. Whether the worsening of LFT elevations during treatment with study drug was due to Xartemis XR is not clear.

The second subject who had LFTs ≥ 10 X ULN was a 22-year-old male (204-037) randomized to Xartemis XR who had normal LFTs at Baseline. At the end of the double-blind period, 48 hours post-bunionectomy, elevated LFTs included ALT (4 x ULN), ALP (1.3 x ULN), AST (4 x ULN), GGT (2.4 x ULN), and LDH (1.2 x ULN). The subject did not enter the OLE, so did not receive any additional doses of Xartemis XR. At a follow-up visit 8 days postbunionectomy (6 days after last dose of Xartemis XR), ALT (12.2 x ULN), ALP (3.2 x ULN), AST (7.1 x ULN), GGT (5.2 x ULN), and LDH (1.5 x ULN) were noted. Two weeks after the Double Blind Period, ALT (3.4 x ULN), ALP (1.8 x ULN), AST (1.2 x ULN), GGT (3 x ULN), and LDH (1.1 x ULN) were decreasing toward the normal reference range, and four weeks following the end of the double-blind period all LFTs were within normal range. This subject had mild increases of LFTs during treatment with Xartemis XR that continued to increase over the following week in the absence of treatment with study drug. These elevations may have been associated with study drug or some other unknown factor, but since they began to increase with treatment, it is likely that Xartemis XR had some causal association.

Dr. Kilgore also conducted an in depth review of the narratives for all cases of hepatic events. She noted one 53 year old female subject (175-030 Study 0181) with a history of cholelithiasis and cholecystectomy who had transient elevation of bilirubin to 1.8 X ULN and transaminase elevations on Day 8 of treatment. Study drug was discontinued on Day 10, by which time the transaminase levels had already begun to decrease and total bilirubin was within normal range. All results (except GGT) returned to normal by Day 20. The course of the laboratory results are shown in the table below. I disagree with Dr. Kilgore that the patient's history of cholelithiasis and cholecystectomy were associated with the increase in transaminase and bilirubin levels. The subject was not reported to have bile duct or underlying liver dysfunction at the time of the study. The abnormal liver function tests may have been related to study drug, even considering the fact that the transaminase levels were already decreasing on the day study drug was discontinued, and total bilirubin was normal, or may have been due to some unknown factor. In any event this case does not meet the criteria for Hy's law, and does not represent a new safety signal for a product containing APAP.

Liver-related laboratory testing Subject 175-030

Test **Reference Range**	**Baseline**	**Day 8**	**Day 10 (Study Drug Stopped)**	**Day 13**	**Day 20**
Alanine Aminotransferase **6.0-34.0U/L**	13 U/L	254 U/L **7.5 X ULN**	155U/L **4.6 X ULN**	54 U/L **1.6 X ULN**	17 U/L
Alkaline Phosphatase **35-123 U/L**	107 U/L	279 U/L **2.3 X ULN**	276 U/L **2.2 X ULN**	171 U/L **1.4 X ULN**	130 U/L 1.1 X ULN
Aspartate Aminotransferase **9-34 U/L**	20 U/L	305 U/L **9 X ULN**	96 U/L **2.8 X ULN**	28 U/L	17 U/L
Bilirubin **3.0-21.0 umol/L**	7 umol/L	38 umol/L **1.8 X ULN**	17 umol/L	7 umol/L	5 umol/L
Direct Bilirubin **0.0-7.0**	2 umol/L	19 umol/L **2.7 X ULN**	9 umol/L **1.3 X ULN**	3 umol/L	2 umol/L
Gamma Glutamyl Transferase **4.0-49.0 U/L**	18 U/L	488 U/L **10 X ULN**	417 U/L **8.5 X ULN**	283 U/L **5.8 X ULN**	141 U/L **2.9 X ULN**
LDH Isoenzyme **53.0-234.0**	231 U/L	450 U/L **1.9 X ULN**	306 U/L **1.3 X ULN**	232 U/L	222 U/L

Adapted from Applicant's Study Report 0181, p. 903

I agree with Dr. Kilgore's conclusions, below, as paraphrased from her review.

- None of the liver function test abnormalities met the criteria for Hy's Law
- Liver enzyme increases were transient for all subjects and returned to normal or near normal
- In general, the hepatic-related safety findings appear consistent with the known safety profile of APAP and do not represent a new safety signal.

The Applicant also conducted an SMQ for Severe Cutaneous Adverse Reactions because of the known association of APAP and these events. Three subjects reported the event of blister. None were severe nor led to discontinuation from the study.

TEAEs of special interest in the Nervous System SOC included dizziness, somnolence, and sedation. Dizziness and somnolence were common TEAEs in the Phase 3 study population and are expected to occur with this drug class.

Fatigue was predefined TEAE of interest, and was reported 1.5% of Xartemis XR treated subjects, which is not unexpected for this drug class

Safety Conclusions

I agree with Dr. Kilgore's conclusions that there were no new or unexpected safety signals detected in the review of the Applicant's data. The safety profile of Xartemis XR is consistent with the opioid class of drugs and APAP. Due to the presence of PEO, the product label should include instructions for use regarding ingestion of adequate water to swallow the pills to prevent choking or obstruction, as well as cautions for use in patients with abnormal GI tracts that may predispose them to GI obstruction.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application.

10. Pediatrics

Under the Pediatric Research and Equity Act (PREA), the Applicant of this NDA is required to conduct pediatric studies for Xartemis XR for the approved indication. The Division's policy regarding opioid analgesics, NSAIDs, and APAP, is that efficacy findings in adults can be extrapolated to pediatric patients down to the age of 2 years, because the underlying condition (pain) and the expected response to these drugs is similar for adults and pediatric patients. Therefore, the requirements for Xartemis XR are to conduct pharmacokinetic and safety studies in patients ages 2 to less than 17 years, and pharmacokinetic, safety, and efficacy studies in patients from birth to two years. Below is the pediatric plan agreed upon by the Division, the Pediatric Research Committee (PeRC), and the Applicant. All studies are deferred because studies in adults are completed and the NDA is currently under review.

Study	**Final Protocol Submission**	**Study Completion**	**Final Report**
Study 1: Open-label study of the PK and safety of Xartemis XR in post-surgical pediatric patients ages 12 to 17 years with moderate to severe acute pain	1/31/14	8/01/15	12/31/15
Study 2: Open-label study of the PK and safety of an age-appropriate formulation of Xartemis XR in pediatric patients ages 2 to 11 years with moderate to severe acute pain	4/1/16	10/01/17	3/01/18
Study 3: PK, safety and efficacy study of an age-appropriate formulation of Xartemis XR in pediatric patients from birth to two years with moderate to severe acute pain	6/01/18	12/01/19	4/01/20

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations conducted clinical inspections of three clinical study sites. The sites were selected for inspection based primarily on large subject enrollment with significant contribution to the overall efficacy outcome. The inspection outcomes are shown below. Two sites have been issued preliminary NAI designations, and at this writing the final inspection outcome is not yet available. However, it appears that the study data from all three

sites are reliable as reported in the NDA. If OSI informs the Division of changes to the outcome designations for the inspections, these will be reflected in the decisional memo.

Clinical Investigator	CDER INDs	Study, Site, & Subjects Enrolled	Inspection Dates & Outcome
Samir J. Azzam, M.D. Anaheim, CA	10	Study 181, Site 166 27 subjects	September 4 - 10, 2013 NAI
Sonia Singla, M.D. Pasedena, CA	26	Study 182, Site 001 89 subjects	October 1 - 9, 2013 Preliminary NAI
Richard A. Pollak, D.P.M. San Antonio, TX	29	Study 182, Site 203 83 subjects	October 8 - 11, 2013 Preliminary NAI

NAI = no action indicated (no significant GCP deviations); **VAI** = voluntary action indicated (significant GCP deviations); **OAI** = official action indicated (serious GCP deviations and/or data unreliable)

Source: OSI review October 17, 2013

Controlled Substance Staff (CSS) Review

The Applicant submitted results from in vivo and in vitro studies to support the abuse-deterrent properties of Xartemis XR and labeling language regarding these properties. (b) (4)

Refer to Dr. Tolliver's review for details regarding the conduct and results of these studies. The following are CSS's conclusions regarding the results of the in vitro and in vivo studies:

(b) (4)

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(b) (4)

[redacted]

12. Labeling

- In an effort to ensure the safe prescribing and use of all opioid products, the language in this label will reflect much of the language now included in the ER/LA opioid labels. This includes modification of the proposed indication in order to better describe the patient population for whom the benefit risk balance is favorable. The exact wording of the indication is being discussed within the Agency and will be reflected in the decisional memo.
- The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name, Xartemis XR, and found it acceptable from both a promotional and safety perspective.
- DMEPA also reviewed the label, labeling and packaging. They provided recommendations to increase the readability and prominence of important information on the label to promote safe use of Xartemis XR. These recommendations have been incorporated into the labeling.
- The Pediatric and Maternal Health Staff was consulted to review labeling for Xartemis XR regarding Sections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers. PMHS was also consulted to provide guidance regarding pediatric labeling of Xartemis XR. The Division and PHMS have agreed upon revisions to the Applicant's proposed labeling that will be included in the approved label.
- The Applicant submitted a Medication Guide, similar in format and content to the ER/LA Medication Guide, that describes the safe use of Xartemis XR and discusses its risks. The Patient Labeling Team (PLT) is currently completing their review, and any recommendations with be included in the MedGuide.
- The label review by OPDP is currently ongoing.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
  I recommend approval for Xartemis XR for management of acute pain where an opioid analgesic is needed. The exact wording of the indication is currently under discussion. I also recommend a dosing regimen of two tablets every 8 to 12 hours for the first dose, followed by every 12 hours for subsequent doses.

- **Risk Benefit Assessment**
  Efficacy was demonstrated for Xartemis XR in one adequate and well-controlled trial in patients with post- operative pain following bunionectomy surgery. Results showed that Xartemis XR was superior to placebo based on the primary endpoint of SPID48. The safety profile of Xartemis XR appears similar to that of oxycodone and acetaminophen, with the most common adverse events being opioid-related. Approximately 2% of Xartemis XR treated patients also showed evidence of transiently elevated transaminase levels, presumably from the APAP component. Because the Xartemis XR formulation includes polyethylene oxide (PEO), which contributes to the extended-release nature of the tablets as well as the intended abuse-deterrent properties, the tablets swell and become sticky when wet. This has the potential to cause choking and GI obstruction (in patients with abnormal GI tracts). The safety database did not include any reports of these events, however as Xartemis XR becomes more widely used, these adverse reactions may occur. Labeling must include appropriate instructions for administration with adequate amounts of water.

  The Applicant submitted in vitro and in vivo studies in support of the abuse-deterrent properties of Xartemis XR, however based on the CSS review, these data are not adequate to support labeling regarding the abuse-deterrent features. As stated in the CSS review, (b) (4)

(b) (4)

(b) (4)

With regards to Xartemis XR, which is an opioid/nonopioid combination product with IR and ER components, contains a relatively low dose of opioid per tablet, and is indicated for acute pain, it would be difficult to pick up a safety signal from these PMRs using postmarketing databases amidst the noise of immediate-release oxycodone/APAP combinations, single entity IR oxycodone and OxyContin. Due to the characteristics of Xartemis XR and proposed acute pain indication for this product its risks appear to be more similar to those of IR opioid products rather than ER, and the postmarketing requirements for the ER/LA opioids indicated for chronic pain are not necessary or appropriate.

Based on the data regarding use and timing of rescue medication following the initial dose of Xartemis XR, and following a discussion with the Applicant regarding this data, I recommend that for the initial dose, language be included in the label that allows a second dose as early as 8 hours for patients require it. Subsequent doses will be labeled as every 12 hours.

Therefore, given the efficacy and safety of Xartemis XR as demonstrated in this NDA, the similarity of this product to immediate-release oxycodone/APAP products in terms of risk, even in the absence of data that supports abuse-deterrent language in the label, the risk benefit balance for this product favors approval. This product appears to be different enough from the ER/LA opioids so that the PMR requirements for ER/LA opioid analgesics should not apply here. Discussions regarding amending the proposed indication in order to better describe the population for whom the risk benefit balance is favorable are currently ongoing within the Agency. The results of this discussion will be reflected in the decisional memo.

(b) (4)

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

  As discussed above, the Agency has determined that Xartemis XR should not be included in the ER/LA REMS due to 1)the low dose of opioid per tablet which is the same as the IR oxycodone/APAP combination, 2) that the formulation includes

both ER and IR components of oxycodone, 3) that the product is combined with APAP so that the labeled dose is limited to mitigate the risk of hepatotoxocity 4) that the inclusion of drug-specific language for Xartemis XR in the ER/LA REMS undermines the messages already in the REMS regarding acute and intermittent use of ER/LA opioids, and 5) that the risks of Xartemis XR appear more similar to IR opioids than ER/LA opioid products. Product labeling, a Medication Guide, and routine pharmacovigilance appear adequate to mitigate the risks of this product.

- **Recommendation for other Postmarketing Requirements and Commitments**

Pediatric studies to fulfill PREA requirements are recommended as follows:

Study	Final Protocol Submission	Study Completion	Final Report
Study 1: Open-label study of the PK and safety of Xartemis XR in post-surgical pediatric patients ages 12 to 17 years with moderate to severe acute pain	1/31/14	8/01/15	12/31/15
Study 2: Open-label study of the PK and safety of an age-appropriate formulation of Xartemis XR in pediatric patients ages 2 to 11 years with moderate to severe acute pain	4/1/16	10/01/17	3/01/18
Study 3: PK, safety and efficacy study of an age-appropriate formulation of Xartemis XR in pediatric patients from birth to two years with moderate to severe acute pain	6/01/18	12/01/19	4/01/20

The Division discussed whether the hyperalgesia study now required as a postmarketing study for approved ER/LA products should be required for Xartemis XR. The purpose of this study is to assess whether patients develop hyperalgesia following long-term use, at least one year, of an ER/LA opioid. Because Xartemis XR is intended for the treatment of acute pain, it does not seem appropriate to require this study, even though Xartemis XR contains an extended-release opioid.

- Recommended Comments to Applicant

None at this time

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

/s/

ELLEN W FIELDS
11/07/2013