CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204031Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	
From	Sharon Hertz, MD, Deputy Division Director
Subject	Abuse Liability Data
NDA#	204031
Applicant	Mallinckrodt, Inc.
Date of Submission	May 28, 2013
PDUFA Goal Date	February 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

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Elizabeth Kilgore, MD, Ellen Fields, MD, MPH
Statistical Review	Feng Li, PhD, Janice Derr, PhD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, R. Daniel Mellon, PhD
CMC Review	Yong Hu PhD, Prasad Peri, PhD
Biopharmaceutics Review	Sandra Suarez, PhD, Angelica Dorantes, PhD
Clinical Pharmacology Review	Wei Qiu, PHD, Yun, Xu, PhD
Controlled Substances Staff	James Tolliver, MD, Silvia Calderon, PHD
OSI	Jong Hoon Lee, Janice Pohlman, MD
CDTL Review	Ellen Fields, MD, MPH
OSE/DMEPA	Vicky Borders-Hemphill, PharmD, Jamie Wilkins parker, PharmD
OSE/DRISK	Danielle Smith, PharmD, MS, Jamie Wilkins Parker, PharmD, Kimberly Lehrfeld, Reema Mehta, PharmD, MPH, BCPS
OPDP/DCDP	Jessica Fox, PharmD
OND/SEALD	Abimbola Adebowale, PhD, Eric Brodsky, MD
OMP/DMPP	
OND/PMHS	Erica Radden, MD, Hari Sachs, MD Leyla Sahin, MD, Jeanine Best, MSN, RN, PNP
CMC Microbiology	John Metcalfe, PhD, Stephen Langille, PhD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
OSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
PMHS= Pediatric and Maternal health Staff
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs
SEALD = Study Endpoints and Labeling Development

1. Introduction

NDA 204031 is 505(b)(2) application for Xartemis XR (oxycodone hydrochloride and acetaminophen) extended-release tablets for the management of [redacted] acute pain, developed under the name COV795. The product contains 7.5 mg of oxycodone and 325 mg of acetaminophen with [redacted]% of the oxycodone [redacted] and [redacted]% of the acetaminophen [redacted] in an immediate-release (IR) layer and [redacted]% of the oxycodone [redacted] and [redacted]% of the acetaminophen [redacted] in an extended-release layer. The intended dosage is two tablets every 12 hours. The approved drug most similar to Xartemis XR is Percocet, immediate-release 7.5 mg oxycodone/ 325 mg acetaminophen tablets (ANDA 40330, Vintage Pharmaceuticals, LLC), a reference listed drug in the Orange Book. However, for the purpose of relying on the Agency's previous findings of safety and efficacy, there are no NDA products that contain oxycodone and acetaminophen so the Applicant relied two Listed Drugs, Roxicodone (NDA 21011, Mallinckrodt, oxycodone 15mg tablets) and Ultracet (NDA 21123, Janssen, tramadol 37.5mg/acetaminophen 325mg).

In addition to differing from approved oxycodone/acetaminophen products by virtue of having extended-release properties, Xartemis XR was formulated with the intention of having abuse-deterrent characteristics through the use of excipients to create physico-chemical barriers to the release of oxycodone following manipulation.

2. Background

The development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an important approach to reducing abuse of prescription opioids.[1] There are different methods for imbuing abuse-deterrent properties to an opioid analgesic and the approach utilized by the Applicant for this formulation was to add excipients to reduce the ability to defeat the extended-release characteristics of Xartemis XR , and to reduce the ability to manipulate the formulation for the purpose of abuse by the intravenous (IV) route of administration. These are generally considered important goals for extended-release opioids that characteristically range to large doses of the active opioid, because manipulating the formulation to release the opioid all at once places individuals at greater risk for overdose and death. Also the abuse of drugs by the IV and intranasal routes of administration is associated with greater risk for overdose resulting from an earlier Tmax and higher Cmax, and IV drug abuse is associated with the risk of contracting bacterial and viral infections, including human immunodeficiency virus.

3. CMC/Device

The two drug substances are supported by DMF 5326 (acetaminophen) and DMF 6930 (oxycodone HCl), both of which were previously reviewed and found to be adequate. Both drug

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

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 ((b) (4) of the impurity (b) (4) (USP related compound (b) (4)), an (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)

The drug product is gastro-retentive tablet formulation composed of a bilayer with immediate-release (IR) and extended-release (ER) properties. The tablet contains 7.5 mg oxycodone HCl with (b) (4) IR layer and (b) (4) ER layer, and 325 mg acetaminophen with (b) (4) IR layer and (b) (4) ER layer. The formulation includes Polyox (b) (4) polyethylene oxide (PEO), as a rate controlling polymer. The viscosity of polyethylene oxide was determined to be a critical material attribute, as the release rate of the drug product is directly impacted by the viscosity of the polymer. The product is intended to swell and remain in the stomach (b) (4). In vitro testing demonstrated that when exposed to several solvents (b) (4) the tablets increased, on average, (b) (4)

Polyethylene oxide has also been used to give the formulation some abuse-deterrent characteristics. (b) (4) the presence of PEO has resulted in the development of a stickiness when wet resulting in the tablet sticking to the wall of the esophagus. Thus, this formulation will be labeled to be taken with at least a cup of water.

The applicant proposed a waiver for exclusion of Microbial Limits testing and a release specification (b) (4) The Applicant's proposal to waive microbial limits testing for product release and stability was found acceptable.

I concur with the conclusions reached by the chemistry reviewer. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months for the 100 count HDPE bottles and 18 months for the 10-count unit dose blister packaging configuration. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

As a 505(b)(2) application, nonclinical data were not required to support the active drug substances as they do not exceed the amount in the referenced products. There are no novel excipients that exceed the amount in previously approved products except for (b) (4) which is adequately by supported data in DMF (b) (4). The drug substance impurities 14-hydroxycodeinone (14-HC) and codeinone (b) (4)

(b) (4) moiety which is a structural alert for genotoxicity. The holder for DMF 6930 for the oxycodone hydrochloride drug substance has shown that 14-HC and codeinone are qualified for genotoxic potential. The current specifications for codeinone and 14-HC proposed by the Applicant for the drug substance are acceptable. The specifications for 6-oxycodol and noroxycodone exceed the thresholds set by ICH Q3A(R2), but both have been shown to be human metabolites of OC. As 6-oxycodol and noroxycodone are produced in the body at levels much greater than the specifications proposed, Dr. Bolan has found that the specifications are acceptable from a pharmacology/toxicology perspective.

The Applicant has identified (b) (4) as drug substance impurities, both with structural alerts, and set the specifications at (b) (4)% and (b) (4)%, respectively. Drug Master File 5326 contains the same specifications for these impurities and has been previously found adequate by the Agency for numerous APAP drug products, and so will be sufficient to support the safety of this product. Dr. Bolan has found the specifications for the impurities in the APAP drug substance acceptable from the pharmacology toxicology perspective.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Eleven pharmacokinetic (PK) studies were conducted in support of this application. The final to-be-marketed tablet with debossed logos was used in two pivotal single-dose and multiple-dose relative bioavailability studies, and a food-effect study which were the focus of the review by Dr. Qiu.

According to Dr. Qiu, the key clinical pharmacology findings were:

1. Xartemis XR 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 XR tablets every 12 hours, steady-state plasma concentrations of oxycodone and acetaminophen were achieved following 1-day administration.

Dr. Qiu also reviewed the human abuse liability study, 244, (b) (4)

Dr. Suarez concluded that the dissolution and acceptance criteria were found acceptable. A proposed in vitro in vivo relationship was found to be unacceptable (b) (4) [redacted] An in vitro analysis demonstrated that exposure to alcohol did not result in loss of the extended-release characteristics.

I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers that there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As the Applicant has submitted a 505(b)(2) application and intends to rely on the Agency's prior findings of efficacy for oxycodone and acetaminophen, and as the combination of oxycodone and acetaminophen in the ratio of 7.5 mg to 325 mg has been previously approved, one efficacy study was required to confirm the efficacy of this novel formulation with both immediate-release and extended-release characteristics. Details of the study can be found in the review by Dr. Kilgore, along with methodology to handle a protocol change after the first 26 subjects were enrolled in the study. In short, this was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients undergoing bunionectomy. A total of 303 subjects (excluding the first 26) were randomized to receive two tabs of either Xartemis XR or placebo every 12 hours once pain was moderate to severe and ibuprofen 400 mg was available as rescue medication.

A total of 269 out of the 303 completed the blinded dosing period with early discontinuations primarily due to adverse events or lack of efficacy. Patients were predominantly female (85%), and white (59%). The prespecified primary efficacy endpoint was the summed pain intensity difference over 48 hours (SPID 48) based on an 11-point numerical rating scale for pain intensity. For the efficacy analysis, pain intensity was measured prior to the use of rescue medication and imputed for the next scheduled assessment within the 6-hour period. Any other scheduled pain assessments that occurred within 6 hours following rescue were censored and imputed by using a multiple imputation approach. The Xartemis-treated subjects had better reduction in pain intensity and used less rescue medication than placebo-treated subjects. Dr. Li evaluated the statistical methods and while he identified several potential statistical issues with the imputation methods used for the primary analysis, he also found that none of the issues affected the statistical conclusions. Dr. Li found that the results of a statistically significant difference in the primary endpoint between Xartemis XR and placebo were not sensitive to the imputation methods employed to handle the pain scores after the use of rescue, or resulting from early discontinuation.

Onset of pain relief, determined by time to confirmed perceptible pain relief (confirmed by meaningful pain relief), was detected by 57% of subjects randomized to Xartemis, compared to 33% of placebo subjects. The median time to onset was 48 minutes for the Xartemis XR group. The mean use of rescue was lower in the Xartemis XR group, 2.9 doses, compared to placebo, 4.6, with 80% and 97% using rescue in the first 12 hours for the Xartemis XR and placebo groups, respectively, and 86% and 99% of patients using at least one dose or rescue during the study for the Xartemis XR and placebo groups, respectively. Time to first use of rescue was 5.8 hours for Xartemis XR for the first 12 hours of the study, but increased to 12 hours for subsequent dosing intervals, supporting the proposed dosing interval of twice daily.

8. Safety

Safety was evaluated in a database consisting of 1028 subjects who received at least one dose of Xartemis. The most informative data came from the efficacy study and from an open-label safety study in patients with osteoarthritis and low back pain. There were two deaths that occurred during the open-label safety study, neither of which appear attributable to study drug. There were six nonfatal serious adverse events, one of which occurred following exposure to placebo. The one serious adverse event which may have been related to study drug was a patient who had vomiting of sufficient severity to result in hospitalization. Early discontinuations due to adverse events within 5 days were most frequently a result of nausea and or vomiting which decreased in frequently with longer duration of use. Among the most common treatment emergent adverse events were nausea, dizziness, headache, vomiting, constipation, somnolence, and rash. In addition, Dr. Kilgore examined treatment emergent adverse events of particular interest for an opioid. There were no respiratory events or hypotension-related adverse events reported. For the nervous and gastrointestinal systems, there were reports of dizziness, somnolence, sedation, constipation, nausea, vomiting, and diarrhea, but not of a frequency that raised concerns for an opioid-containing analgesic. Additional safety analyses can be found in Dr. Kilgore's review.

(b) (4)

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9. Advisory Committee Meeting

No advisory committee was convened for this application.

10. Pediatrics

Consultation was obtained from PMHS for the proposed pediatric study plan and the proposed labeling. As noted by Dr. Fields:

> 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.

Additionally, PHMS summarized the relevant literature concerning the use of oxycodone and acetaminophen during pregnancy and breastfeeding, and provided revisions for the Pregnancy and Nursing Mothers sections of the package insert.

11. Other Relevant Regulatory Issues

Clinical Site Inspections

The Office of Scientific Investigations inspected three clinical study sites, selected based primarily on large subject enrollment. Two sites received an inspection outcome as preliminary NAI, the third, NAI. The review states that the observations noted for the inspections are based on the preliminary review of the Establishment Inspection Reports. OSI will generate an inspection summary addendum if conclusions change upon OSI final classification. OSI classification of inspection is finalized when written correspondence is issued to the inspected entity. If the classification does not differ from the preliminary classification included in the clinical inspection summary, no statement with a final recommendation is issued.

Risk Evaluation and Mitigation Strategy (REMS)

At the time of NDA submission, the Application included a proposed REMS which integrated Xartemis XR into the approved Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS, based on discussions during development. Based on review of the proposed REMS in conjunction with OSE's Division of Risk Management, it became apparent that inclusion of a Xartemis XR with an acute pain indication in the ER/LA REMS would undermine the two key educational messages of the ER/LA REMS, that ER/LA products are indicated for chronic use and are not intended for acute pain that could be managed with other products, and that ERLA products for chronic pain are not for use on an intermittent basis. An additional complication was that the postmarketing requirement (PMR) for the ER/LA opioids for chronic pain negotiated under the safety labeling changes provisions of FDAAA would not apply to Xartemis XR as the epidemiologic studies require data from chronic use of the medications. Consideration was then given to whether any REMS was necessary to ensure the safe use of Xartemis. Although the formulation has extended-release characteristics, the amount of oxycodone in each tablet is 7.5 mg, the same as available in immediate-release combination oxycodone and acetaminophen products. As a result, even if individuals were to mistakenly or intentionally attempt to defeat the extended-release characteristics of Xartemis, the amount of oxycodone would not exceed the amount available in an immediate-release product. Furthermore, the total daily dose of oxycodone from Xartemis XR has the same limitations as immediate-release combination oxycodone and acetaminophen products in order to avoid exceeding the safe daily limit of acetaminophen. The overall risks associated with Xartemis XR are comparable to immediate-release combination oxycodone and acetaminophen products than to the products included in the ER/LA opioid REMS. Therefore, it was concluded that there was no need for a REMS for this product. However, there was internal agreement that, as an extended-release opioid formulation, the labeling for Xartemis XR will include the updated language added to existing extended-release opioid medications.

As noted in Dr. Kilgore's review, the Applicant provided adequate financial disclosure information and no impropriety was identified.

12. Labeling

The package insert was amended to reflect most of the updated labeling recently required for the labeling of ER/LA opioid analgesics. The rationale for implementing these changes is based on providing prescribers with information they can use to balance risk along with benefit when prescribing opioid analgesics. For example, the emphasis on balancing safety is reflected in the addition of a boxed warning for addition, abuse and misuse; life-threatening respiratory depression; accidental exposure; neonatal opioid withdrawal syndrome; and hepatotoxicity. This emphasis is also reflected in the indication which was changed from (b) (4) to "the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate", and with a limitations of use statement as follows:

> 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.

A medication guide based on the ER/LA opioid analgesics has also been added.

The dosage and administration section calls for dosing two tablets every 12 hours and allows for the second dose to be administered as early as 8 hours after the initial dose if needed.

Recommendations for the package insert from Dr. Adebowale of SEALD and recommendations for the package insert and the medication guide from Dr. Fox of OPDP were conveyed to the Applicant and implemented.

Recommendations from Dr. Borders-Hemphill for the package insert and container and carton labeling were conveyed to the Applicant and implemented.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment
  The Applicant has adequately demonstrated that the efficacy of Xartemis XR outweighs the risks when used to treat acute pain in the population studied. The product is the first combination opioid and acetaminophen with extended-release characteristics, and this formulation also has immediate-release characteristics. The strength, 7.5 mg of oxycodone and 325 mg of acetaminophen, is comparable to available strengths of immediate-release combination oxycodone and acetaminophen, and the dosing regimen of two tablets every 12 hours is well within the dosing limits of these products as well.

  The importance of understanding the risk associated with opioid analgesics when deciding when to prescribe these products has been emphasized in improved

safety language throughout the package insert, including new boxed warnings, an amended indication, and the addition of a medication guide.

- Recommendation for Postmarketing Risk Management Activities
  None

- Recommendation for other Postmarketing Study Commitments

  2131-1 Conduct an open-label pharmacokinetics and safety study of Xartemis XR in pediatric patients ages 12 to less than 17 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

  Final Protocol Submission: April 30, 2014
  Study/Trial Completion: November 1, 2015
  Final Report Submission: March 31, 2016

  2131-2 Conduct an open-label pharmacokinetics and safety study of an age-appropriate formulation (oxycodone hydrochloride/acetaminophen) in pediatric patients ages 2 to less than12 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

  Final Protocol Submission: July 1, 2016
  Study/Trial Completion: January 1, 2018
  Final Report Submission: June 1, 2018

  2131-3 Conduct a pharmacokinetics, safety, and efficacy study of an age-appropriate formulation (oxycodone hydrochloride/acetaminophen) in pediatric patients ages 0 (birth) to less than 2 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

  Final Protocol Submission: September 1, 2018
  Study/Trial Completion: March 1, 2020
  Final Report Submission: July 1, 2020

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/s/

SHARON H HERTZ
03/11/2014