

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204031Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204031	NDA Supplement #: Not applicable (n/a)	Efficacy Supplement Type SE- n/a
Proprietary Name: Xartemis XR Established/Proper Name: oxycodone hydrochloride and acetaminophen Dosage Form: extended-release oral tablet Strengths: 7.5 mg/325 mg		
Applicant: Mallinckrodt Inc.		
Date of Receipt: May 28, 2013		
PDUFA Goal Date: February 28, 2014		Action Goal Date (if different): March 3, 2014
RPM: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager		
Proposed Indication(s): Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Listed drug, Percodan (aspirin/oxycodone hydrochloride) tablets, 325 mg/4.8355 mg, NDA 007337	Safety and efficacy of oxycodone hydrochloride, including Sections 1, 5, 7, 8, 9, 12, and 13 of package insert
Listed drug, Ultracet (tramadol hydrochloride/acetaminophen) tablets, 37.5 mg/325 mg, NDA 021123	Safety and efficacy of acetaminophen, including Sections 1, 5, 7, 8, 10, and 12 of package insert
Published literature	7.4 Agents Affecting Cytochrome P450 Enzymes 8.1 Pregnancy 8.3 Nursing Mothers 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Bioavailability comparisons were conducted to establish a scientific bridge between Xartemis XR and drug products, Roxicodone and Ultracet, for oxycodone hydrochloride exposure and acetaminophen exposure respectively. Roxicodone (NDA 021011) is owned by the sponsor, Mallinckrodt, Inc, and was approved via the 505(b)(2) pathway with Percodan as the listed drug, with an appropriate scientific bridge between Roxicodone and Percodan. Roxicodone is an appropriate product for BA/BE comparisons with Xartemis XR for oxycodone hydrochloride exposure.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐
If "NO," proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒
If "NO", proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Percodan (aspirin/oxycodone hydrochloride) tablets	NDA 007337	Y
Ultracet (tramadol hydrochloride/acetaminophen) tablets	NDA 021123	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: Roxicodone, NDA 021011

b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This product provides for a new dosing regimen, i.e., 12-hour dosing.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

Note: The exact wording of the indication for Xartemis XR differs from the listed products due to our interest in emphasizing that the product is for “acute pain severe enough to require an opioid...” rather than for “moderate to severe acute pain”; however, the general indication of acute pain is the same.

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

If this application relies only on non product-specific published literature, answer “N/A”

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): **There are many ANDA-approved products that are listed in the Orange Book and are pharmaceutical alternatives to Xartemis XR. However, there are no NDA-approved pharmaceutical alternatives.**

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

DOMINIC CHIAPPERINO
03/03/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 204031/Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablet

PMR Description: Deferred pediatric study under PREA: 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.

PMR Schedule Milestones:	Final Protocol Submission:	4/30/2014
	Study/Trial Completion:	11/1/2015
	Final Report Submission:	3/31/2016
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics and safety 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) for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To obtain adequate data to describe the dosing and safety 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. This is not a FDAAA PMR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics and safety 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. The study can be an open-label trial.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Pharmacokinetic and safety study
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 204031/Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablet

PMR Description: Deferred pediatric study under PREA: Conduct an open-label pharmacokinetics and safety study of an age-appropriate formulation of Xartemis XR in pediatric patients ages 2 to less than 12 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

PMR Schedule Milestones:	Final Protocol Submission:	7/1/2016
	Study/Trial Completion:	1/1/2018
	Final Report Submission:	6/1/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics and safety of an age-appropriate oxycodone hydrochloride/acetaminophen formulation in pediatric patients ages 2 to less than 12 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate) for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To obtain adequate data to describe the dosing and safety of the oxycodone hydrochloride/acetaminophen combination in pediatric patients ages 2 to less than 12 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics and safety of Xartemis XR in pediatric patients ages 2 to less than 12 years with acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. The study can be an open-label trial.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
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Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Pharmacokinetic and safety study
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Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 204031/Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablet

PMR Description: Deferred pediatric study under PREA: Conduct a pharmacokinetics, safety, and efficacy study of an age-appropriate formulation Xartemis XR 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.

PMR Schedule Milestones:	Final Protocol Submission:	9/1/2018
	Study/Trial Completion:	3/20/2020
	Final Report Submission:	7/1/2020
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics, safety, and efficacy of the oxycodone hydrochloride/acetaminophen combination in pediatric patients from 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) for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

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– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics, safety, and efficacy of the oxycodone hydrochloride and acetaminophen combination with an age-appropriate formulation in pediatric patients from 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.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Pharmacokinetic, safety, and efficacy studies or clinical trials
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DOMINIC CHIAPPERINO
02/27/2014

JUDITH A RACOOSIN
02/27/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title ¹	XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets, for oral use, CII
Applicant	Mallinckrodt LLC
Application/Supplement Number	NDA 204031
Type of Application	Original
Indication(s)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.
Office/Division	ODEII/DAAAP
Division Project Manager	Dominic Chiapperino
Date FDA Received Application	May 28, 2013
Goal Date	February 28, 2014
Date PI Received by SEALD	February 21, 2014
SEALD Review Date	February 24, 2014
SEALD Labeling Reviewer	Abimbola Adebawale
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL > one-half page. DAAAP will grant a waiver in the approval letter.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is no white space present before the Product Title heading and the Boxed Warning in HL. Insert white space before both headings.*

There is white space between the HL heading and the HL Limitation Statement in HL. Delete the white space because there must be no white space between the HL heading and HL Limitation Statement.

Selected Requirements of Prescribing Information

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment: *Boxed Warning length is 23 lines instead of 20 lines. DAAAP stated that they need to keep all the current text in the Boxed Warning because it is class labeling.*

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

Selected Requirements of Prescribing Information

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

Selected Requirements of Prescribing Information

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: *The subsection heading “12.1 Mechanism of Action” in the TOC does not match the subsection heading “12.1 MECHANISM OF ACTION” in the FPI. Match the TOC and FPI subsection headings.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment: *The statement “*Sections or subsections omitted from the full prescribing information are not listed” at the end of the TOC does not need to be bolded as shown above.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS

Selected Requirements of Prescribing Information

4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Subsection heading currently written as “12.1 MECHANISM OF ACTION” should read as “12.1 Mechanism of Action” as shown in the table above.

Subsection heading “8.2 Labor or Delivery” is currently underlined. As shown in the table above this subsection heading should not be underlined. Delete underline.

NO

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

Comment: In subsection 9.3 “Dependence”, the cross-reference currently written as “[see Use in Special Populations (8.1, 8.2)]” should read as “[see Use in Specific Populations (8.1, 8.2)]” i.e., correct the section heading.

Also in subsection 12.3 “Pharmacokinetics” under subheadings “Hepatic Impairment” and “Renal Impairment”, the cross-reference currently written as “[see Use in Special Populations (8.6)]” and “[see Use in Special Populations (8.7)]” respectively, should read as “[see Use in Specific Populations (8.6)]” and “[see Use in Specific Populations (8.7)]”, respectively.

N/A

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

Selected Requirements of Prescribing Information

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

Selected Requirements of Prescribing Information

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABIMBOLA O ADEBOWALE
02/24/2014

ERIC R BRODSKY
02/24/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.



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

Date: February 14, 2014

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 204-031 Supplement, Xartemis XR (MNK795) (Oxycodone HCl and Acetaminophen (b) (4) Tablets)
Indication: Management of (b) (4) pain
Dosages: 7.5 mg Oxycodone HCl/325 mg Acetaminophen (APAP)
Sponsor: Mallinckrodt Inc.

Materials reviewed: Reports submitted by Sponsor under sequence numbers 0012, 0014, 0016, and 0017 for NDA 204-031

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1 Background

This memorandum consists of a review, with conclusions and recommendations, by CSS of supplemental data provided by Mallinckrodt Inc. for MNK795 (oxycodone HCl/acetaminophen) (b) (4) Release Tablets under NDA 204031. This review was requested by the Division of Anesthesiology, Analgesia, and Addiction Products (DAAAP) regarding possible abuse deterrent claims in the label.

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/s/

JAMES M TOLLIVER
02/14/2014

SILVIA N CALDERON
02/14/2014

MICHAEL KLEIN
02/14/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: February 3, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, Pharm.D, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Xartemis XR (Oxycodone Hydrochloride and
Acetaminophen Extended Release Tablets), 7.5 mg/325 mg

Application Type/Number: NDA 204031

Applicant: Mallinckrodt Inc.

OSE RCM #: 2013-1271

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This memorandum evaluates the revised container labels and carton labeling for Xartemis XR (oxycodone hydrochloride and acetaminophen extended release tablets), 7.5 mg/325 mg submitted November 23, 2013 and January 22, 2014 (see Appendices A and B). The Division of Medication Error and Prevention Analysis (DMEPA) initially reviewed the container labels in OSE review 2013-1271, dated October 11, 2013.

2 MATERIALS REVIEWED

DMEPA evaluated the revised container labels and carton labeling submitted November 23, 2013, and January 22, 2014. We compared the revised labels and labeling against our recommendations in OSE Review 2013-1271, dated October 11, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMENDATIONS

We find the revisions acceptable; therefore, we have no further recommendations at this time.

If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRENDA V BORDERS-HEMPHILL
02/03/2014

IRENE Z CHAN
02/03/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 7, 2013

To: Dominic Chiapperino, PhD
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products

From: Jessica Fox, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 204031
XARTEMIS XR (oxycodone hydrochloride and acetaminophen)
Extended-Release Tablets, for oral use, CII

As requested in the Division of Anesthesia, Analgesia, and Addiction Products' (DAAAP) consult dated August 23, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the XARTEMIS XR prescribing information, carton/container labeling, and medication guide.

OPDP's comments on the prescribing information are provided below in the proposed substantially complete version of the prescribing information sent via email by DAAAP on October 24, 2013.

OPDP has reviewed the carton/container labeling submitted by the sponsor on August 23, 2013, and accessed via <\\CDSESUB1\evsprod\NDA204031\204031.enx>, and has no comments at this time.

The Division of Medical Policy Programs and OPDP have provided a single, consolidated review of the medication guide that was entered into DARRTS on November 7, 2013.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
11/07/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 7, 2013

To: Bob A. Rappaport, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills , BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jessica M. Fox, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): XARTEMIS XR (oxycodone hydrochloride and acetaminophen)

Dosage Form and Route: Extended-Release tablets, for oral use, CII

Application Type/Number: NDA 204031

Applicant: Mallinckrodt, Inc.

1 INTRODUCTION

On May 28, 2013, Mallinckrodt, Inc. submitted for the Agency's review a 505 (b)(2) New Drug Application (NDA) 204031, for XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets. The proposed indication for XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is for the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. The Applicant states in their cover letter dated May 24, 2013, that this 505(b)(2) NDA relies on the FDA's findings of safety and efficacy of two Reference Listed Drugs (RLDs), Roxicodone, NDA 021011 (Mallinckrodt) and Ultracet, NDA 021123 (Janssen Pharms).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on August 23, 2013, for DMPP and OPDP to review the Applicant's proposed for XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release tablets Medication Guide (MG) received on May 28, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2013.
- Draft XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release tablets Prescribing Information (PI) received on May 28, 2013 and further revised by the Applicant and the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/07/2013

JESSICA M FOX
11/07/2013

BARBARA A FULLER
11/07/2013

LASHAWN M GRIFFITHS
11/07/2013



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

Date: November 4, 2013

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 204-031, COV795 (also called NMK795) (Oxycodone HCl and Acetaminophen (b) (4) Tablets)
Indication: Management of (b) (4) acute pain
Dosages: 7.5 mg Oxycodone HCl / 325 mg Acetaminophen (APAP)
Sponsor: Mallinckrodt Inc.

Materials reviewed: 1) (b) (4) Final Report, dated December 9, 2011, and entitled "Abuse Deterrence Evaluation (b) (4) (Oxycodone HCl 7.5 mg /APAP 325 mg Gastro-Retentive Tablets) in Comparison to Percocet Tablets." (Module 3.2.P.1)
2) Report entitled "Oxycodone HCl and Acetaminophen ER Tablets (NMK795) Assessment of Intravenous Abuse Potential" provided October 17, 2013 (Supplement 007)
3) Clinical Study Report (b) (4) 244

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/s/

JAMES M TOLLIVER
11/04/2013

SILVIA N CALDERON
11/04/2013

MICHAEL KLEIN
11/04/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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**PEDIATRIC AND MATERNAL HEALTH STAFF,
MATERNAL HEALTH TEAM REVIEW**

Date: 10-28-2013

From: Leyla Sahin, M.D.
Medical Officer,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Lynne P Yao, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia and Addiction Products

Drug: Xartemis XR (oxycodone/acetaminophen); NDA 204031

Applicant: Mallinckrodt

Subject: Labeling for Pregnancy and Nursing Mothers

Materials Reviewed: Applicant labeling, literature review

Consult Question: Please review the proposed labeling for Pregnancy and Nursing Mothers

INTRODUCTION

Mallinckrodt submitted a 505(b) (2) application on May 24, 2013 for Xartemis XR® (7.5 mg oxycodone hydrochloride and 325 mg acetaminophen) (b) (4) release tablets for the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. (b) (4).

The referenced listed drugs, Roxycodone® (15 mg oxycodone) and Ultracet® (37.5 mg tramadol and 325 mg acetaminophen), were approved in 2000 and 2001, respectively. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's (PMHS-MHT) review of the sponsor's proposed labeling for Pregnancy and Nursing Mothers. PMHS-MHT performed a literature review of acetaminophen and oxycodone use in pregnancy and breastfeeding. This review summarizes available data, and provides conclusions and recommendations regarding Pregnancy and Nursing Mothers labeling for Xartemis XR.

BACKGROUND

Oxycodone is a semisynthetic opioid analgesic. Xartemis XR is an extended-release tablet for oral administration containing both immediate-and extended-release components. Xartemis XR utilizes a delivery technology that is designed to swell in gastric fluid and gradually release the remainder of oxycodone and acetaminophen to the upper gastrointestinal tract.

Opioid medications may be needed during pregnancy to manage severe pain associated many conditions, including both acute and chronic medical conditions and surgical procedures. Recent studies show that the prevalence of opioid use among pregnant women ranges from 2% to 20%, and usage of opioids in pregnancy has been increasing.^{1, 2}

REVIEW OF DATA

Literature Review of Acetaminophen

Pregnancy

This reviewer had previously reviewed the literature on acetaminophen exposure in pregnancy for the NDA for intravenous acetaminophen, Ofirmev (see review in DARRTS dated 2-9-2010). The previous review evaluated two large population based studies^{3,4} and did not show an increased risk of congenital malformations following acetaminophen exposure. Study findings

¹ Epstein RA, Bobo WV, Martin PM, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Annals of Epidemiology* 2013; 12: 498-503.

² Epstein RA, Ray WA, Bobo WV, et al. Increasing first trimester use of opioid analgesics. *Pharmacoepidemiology Drug Safety* 2012; 21(suppl 3): 370.

³ Feldkamp M, Meyer R, Krikov S, et al. Acetaminophen Use and Risk of Birth Defects. *Obstetrics and Gynecology* 2010; 115 (1):109-115.

⁴ Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. *Am J Obstet Gynecol* 2008; 198:178.e1-178.e

that showed an association with childhood asthma were inconsistent. Since the date of the previous review, three new studies have been published, which are reviewed below.

1. A Dutch prospective, observational study that included 3,184 women with male infants showed a positive association with cryptorchidism following second trimester exposure to acetaminophen: adjusted OR 1.89 (95% CI 1.01-3.51), based on 15 exposed cases.⁵ There was no positive association with cryptorchidism following first or third trimester of exposure.

The authors acknowledge that this study is limited by the small number of exposed cases, lack of information on dose and duration of use, and the lack of adjustment for important confounders such as prematurity, family history, and concomitant exposures.

Reviewer comments

Cryptorchidism is the most common congenital abnormality in male infants and there is controversy regarding the timing of the descent of the testes during fetal development.⁶ Some describe descent between weeks 8 and 14 of gestation, whereas others note that descent occurs between weeks 10 and 23, or in the last trimester.^{6,7,8} Risk factors for cryptorchidism include prematurity and family history, which were not adjusted for in this study. In addition, 75% of cases resolve within 3 months of birth, and this study did not assess whether there was resolution of the cryptorchidism.

2. A prospective cohort study performed as part of the Danish National Birth Cohort⁹ that included 22,449 infant boys who had been exposed to acetaminophen in utero showed no statistically significant association between acetaminophen use during any trimester or gestational weeks 8 and 14 and cryptorchidism. In the numerous analyses on the effect of duration of use, the only association that was statistically significant was an association between acetaminophen exposure for greater than 4 weeks during gestational weeks 8-14 and cryptorchidism (adjusted hazard ratio 1.38, 95% confidence interval 1.05-1.83); however there was no corresponding increase in orchiopexies. The effect of duration of use was not evaluated at other gestational times.

Reviewer comments

The fact that there was no increase in corresponding orchiopexies may indicate that the cryptorchidism cases resolved or did not have clinical significance. In addition, the fact that a

⁵ Snijder CA, Kortenkamp A, Steegers EAP, et al. Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadias in the offspring: the Generation R study. *Human Reproduction* 2012; Vol 27, No. 4:1191-1201.

⁶ Toppari J, Virtanen V, Main KM, et al. Cryptorchidism and Hypospadias as a Sign of Testicular Dysgenesis Syndrome: Environmental Connection. *Birth Defects Research (Part A)* 2010; 88:910-919.

⁷ Hutson JM, Hasthorpe S, Heyns CF. Anatomical and functional aspects of testicular descent and cryptorchidism. *Endocr Rev* 1997; 18:259-280.

⁸ Foresta C, Zuccarello D, Garolla A, Ferlin A. Role of hormones, genes, and environment in human cryptorchidism. *Endocr Rev* 2008; 29:560-580.

⁹ Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sorensen HT, Bonde JP, Henriksen TB, Olsen J. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology* 2010; 21:779-785.

statistically positive association with cryptorchidism was found only in the group that had exposure for greater than 4 weeks during gestational weeks 8-14 may be confounded by the underlying indication, such as a chronic disorder, or confounded by concomitant exposures.

3. Another Danish group performed a prospective cohort study of Danish and Finnish pregnancies and reported no statistically significant association between acetaminophen use during the first or second trimester and cryptorchidism (use during the third trimester was not assessed).¹⁰ In an analysis of the effect of duration of use, there was a statistically significant association with exposure for longer than 2 weeks in the first and second trimester and cryptorchidism (adjusted odds ratio 2.78, 95% confidence interval 1.13-6.84). There were no positive associations seen for acetaminophen use and cryptorchidism in the Finnish cohort.

Reviewer comments

This study's findings are inconsistent as the positive finding in the Danish cohort was not seen in the Finnish cohort. Also, the fact that a statistically positive association with cryptorchidism was found only in the group that had exposure for greater than 2 weeks in the first and second trimester may be confounded by the underlying indication, such as a chronic disorder, or confounded by concomitant exposures.

Reviewer's assessment of available data on acetaminophen exposure in pregnancy and cryptorchidism

This reviewer had previously reviewed a prospective cohort study conducted using the Danish National Birth Cohort, a population-based study that enrolled 101,041 pregnant women from 1996 to 2003, that found no increased risk of cryptorchidism following first trimester exposure to acetaminophen, based on 33 exposed cases.⁴

The three recently published studies on acetaminophen exposure during pregnancy and cryptorchidism have inconsistent findings and may be confounded by indication, concomitant exposures, and lack of adjustment for other important confounders such as family history and prematurity. Therefore available data on the use of acetaminophen during pregnancy and cryptorchidism are confounded and inconsistent, and do not allow any conclusions to be drawn.

Lactation

This reviewer had previously reviewed the literature on the presence of acetaminophen in human milk for the NDA for intravenous acetaminophen, Ofirmev (see review in DARRTS dated 2-9-2010). The previous review evaluated data from 19 breastfeeding women showed that acetaminophen was present in small quantities in human milk. This information is in the currently approved labeling for Ofirmev. There are no new publications on acetaminophen and breastfeeding.

¹⁰ Kristensen DM, Hass U, Lesne L, Lottrup G, et al. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum Reprod 2011 Jan; 26(1):235-44.

Literature Review of Oxycodone Pregnancy

Two case-control studies conducted in the U.S. by the Centers for Disease Control (CDC) National Birth Defects Prevention Study (NBDPS)¹¹ and the Slone Epidemiology Center Birth Defects Study (BDS)¹² reported statistically significant associations between opioid exposure in the first trimester of pregnancy and congenital malformations.

The NBDPS showed a positive association between oxycodone use and pulmonary valve stenosis based on 8 cases: crude OR 2.4 (1.1-5.4). Adjustment for potential confounders such as maternal age, obesity, race, education and smoking, was not done due to the limited sample size.

The BDS showed a positive association between opioid use and spina bifida based on 10 cases: adjusted OR 2.2 (1.1-4.1). An analysis of individual opioids was not done based on the small sample size. The mean duration of opioid use was almost 3 months in the case group and the control groups (included a nonmalformed group and a group of infants with malformations other than neural tube defects).

Reviewer comments

Both studies are limited by recall bias (interviews were conducted with mothers up to 3 years after giving birth), the small number of exposed cases, and the lack of adjustment for multiple statistical analyses, which may result in in chance findings. Furthermore, the prolonged duration of use of opioids in all three arms of the BDS may not be representative of the expected duration of use of Xartemis XR and therefore the study findings may not be generalizable to the anticipated population of typical users.

Studies which have shown no increased risk of congenital malformations following first trimester exposure to oxycodone include the following:

- A case control study based on 5 cases exposed to oxycodone¹³
- A prospective observational study of 78 women who were exposed to oxycodone¹⁴
- The National Institutes of Health Collaborative Perinatal Project, a case control study of 58, 282 mother-child pairs, which included 8 women exposed to oxycodone.¹⁵

Reviewer comments

¹¹ C.S. Broussard, S.A. Rasmussen, J. Reefhuis et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol, 204 (2011), pp. 314.e1–314.e11

¹² Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional Use of Opioids and the Risk of Neural Tube Defects. Obstetrics and Gynecology. 2013 (122):4:838-844.

¹³ Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol 1981; 58:336–44.

¹⁴ Schick B, Hom M, Tolosa J, Librizzi R, Donnenfeld A. A preliminary analysis of first trimester exposure to oxycodone and hydrocodone. Reprod Toxicol. 1996;10:162.

¹⁵ Heinonen OP, Slone D, Shapiro S. Analgesics and antipyretic drugs. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group Inc; 1977. p. 286–95.

The cumulative data on oxycodone exposure during pregnancy and congenital malformations very limited; therefore it is not possible to draw any conclusions regarding the risks of malformations following exposure to oxycodone during pregnancy.

Lactation

In a study of six breastfeeding mothers who were taking 1 to 2 capsules containing a combination of 5 mg oxycodone and 500 mg acetaminophen every 4 to 7 hours for post-cesarean section pain, colostrum samples were obtained several times after successive doses.¹⁶ Peak oxycodone milk levels occurred 1 to 2 hours after the first dose and then at variable times after successive doses. Oxycodone could be measured in milk up to 4, 12, and 36 hours after 4, 9, and 11 doses respectively. Oxycodone milk levels ranged from undetectable (<5 mcg/L) to 229 mcg/L. The authors estimated that an exclusively breastfed neonate would receive a maximum 8% of the maternal weight-adjusted dosage of oxycodone.

Reviewer comments

Although the estimated infant exposure to 8% of the maternal weight-adjusted dosage of oxycodone is less than the limit of 10% of the maternal weight adjusted dose that is cited in a published reference regarding the use of drugs in breastfeeding¹⁷, this amount is probably an underestimation as active metabolite levels were not measured, and the calculated estimation regarding the amount of drug in breast milk based on colostrum levels may not be true for mature milk.

In a study of fifty mothers who delivered by cesarean section and received oxycodone, colostrum and serum samples were measured at 24, 48 and 72 hours postpartum without respect to the time of the previous oxycodone dose.¹⁸ The most common doses received by the mothers during the previous 24 hours (including one 30 mg dose rectally immediately post-surgery in some cases) were 60 mg (range 30 to 90 mg), 40 mg (range 0 to 90 mg), and 20 mg (range 0 to 50 mg), respectively. Mean colostrum concentrations at the 3 collection times were 58 mcg/L (range 7 to 130 mcg/L), 49 mcg/L (range 0 to 168 mcg/L), and 35 mcg/L (range 0 to 31 mcg/L), respectively. Colostrum concentrations were 3.2 to 3.4 higher than maternal serum levels. Five women had detectable oxycodone in milk 37 hours after the last dose. A total of 45 blood samples were taken from 41 breastfed infants at 24, 48 or 72 hours postpartum. Only 1 of the samples had a detectable (>2 mcg/L) oxycodone level of 7.4 mcg/L.

Reviewer comments

These data suggest that oxycodone concentrates in milk. It is of clinical significance that oxycodone persisted in breast milk up to 37 hours after the last dose. This study did not sample milk at peak times (1-2 hours post-dose), therefore the peak drug levels in milk are probably underestimated.

¹⁶ Marx CM, Pucino F, Carlson JD et al. Oxycodone excretion in human milk in the puerperium. Drug Intell Clin Pharm. 1986; 20:474. Abstract.

¹⁷ Hale T. Medications and Mothers' Milk. 2012. Fifteenth Edition.

¹⁸ Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: Relationships between maternal plasma, breast milk and neonatal plasma levels. Aust N Z J Obstet Gynaecol. 2007; 47:181-5.

In a retrospective study, 139 nursing mothers who were taking either oxycodone, codeine or acetaminophen for post-partum pain were contacted by telephone to determine the degree of maternally perceived central nervous system (CNS) depression.¹⁹ Mothers taking oxycodone reported signs of CNS depression in 20% of their infants, while those taking codeine and acetaminophen reported infant CNS depression in 17% and 0.5%, of their infants, respectively.

There is a case report of a breastfeeding newborn infant who had opioid intoxication due to maternal use of oxycodone following cesarean section.²⁰ The newborn infant was exclusively breastfed and found to be well by his physician at 4 days postpartum. Later on the same day, the infant became sedated, became difficult to arouse and did not feed from either breast. The infant was brought to the emergency department where the infant was found to have lethargy, hypothermia, pinpoint pupils, and a poor sucking reflex. The mother reported that her milk had come in the previous evening. She had taken 10 mg of oxycodone that evening and another 5 mg the next morning in the form of Percocet (oxycodone 5 mg plus acetaminophen 325 mg). The infant was given naloxone 0.34 mg intramuscularly and within 2 minutes, the baby's eyes opened and he drank 45 mL of formula. No further sedation was seen over the next 24 hours. The reporting physician concluded that the infant's opioid intoxication was caused by oxycodone in breastmilk.

Reviewer comments

It is concerning that oxycodone persisted in breast milk up to 37 hours after the last dose. Neonates' clearance rates of oxycodone vary significantly²¹, therefore there may be potential for accumulation and toxicities such as sedation and respiratory depression, as seen in one published study and the case report. Available data are limited by the lack of data collected on oxycodone's active metabolites noroxycodone and oxymorphone, and the lack of data on drug levels in milk after the first 72 hours when colostrum is replaced by milk; therefore it is not possible to accurately quantify the levels in human milk. Based on this reviewer's assessment of available data, PMHS-MHT concurs with the American Academy of Pediatrics Committee on Drugs not recommending oxycodone use in the lactating mother.²²

LABELING

Applicant's proposed labeling

The following is the applicant's proposed labeling for Xartemis XR:

8.1 Pregnancy

Pregnancy Category C

¹⁹ Lam J, Kelly L, Ciszowski C et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. J Pediatr. 2012;160:33-37.e2.

²⁰ Timm NL. Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. J Pediatr. 2013;162:421-2.

²¹ Pokela ML, Anttila E, Seppala T et al. Marked variation in oxycodone pharmacokinetics in infants. Paediatr Anaesth. 2005; 15:560-5.

²² Sachs HC. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on selected topics. Pediatrics 2013;132(3).

DISCUSSION AND CONCLUSIONS

The cumulative data on oxycodone exposure during pregnancy and congenital malformations are very limited; therefore it is not possible to draw any conclusions regarding the risks of malformations following exposure to oxycodone during pregnancy. PMHS-MHT recommends including a statement to the Risk Summary that states that the incidence of malformations in human pregnancies has not been established for oxycodone as the data are limited.

Two large population based studies on acetaminophen exposure in pregnancy have not shown an increased risk for congenital malformations overall or specific malformations. The data on acetaminophen exposure in pregnancy and cryptorchidism are confounded and inconsistent, and do not allow any risk conclusions to be drawn. PMHS-MHT concurs with the applicant's proposal to include a statement that two large population based studies on acetaminophen exposure in pregnancy have not shown an increased risk for congenital malformations. PMHS-MHT had discussions with DAAAP regarding the content of the Pregnancy subsection of labeling. In concurrence with the DAAAP reviewers, PMHS-MHT agrees that the proposed regulatory language under Pregnancy, "Xartemis should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus," adequately reflects the risk –benefit profile regarding use in pregnancy.

Acetaminophen is present in small quantities in human milk. Available lactation data show that oxycodone is present in human milk; however it is not possible to accurately quantify the levels. Variations in neonates' clearance rates may result in accumulation and toxicities such as sedation and respiratory depression. PMHS-MHT had discussions with DAAAP regarding the content of the Nursing Mothers subsection of labeling. In concurrence with the DAAAP reviewers, PMHS-MHT agrees that the proposed regulatory language, "Discontinue nursing or discontinue drug taking into (b) (4) the importance of the drug to the mother."

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance,

PMHS-MHT is structuring the Pregnancy and Nursing mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the labeling, not the amount.

LABELING RECOMMENDATIONS

These revisions were agreed upon by PMHS-MHT and DAAAP.

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and/or well-controlled studies with Xartemis XR tablets or oxycodone/acetaminophen in pregnant women. Epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. The incidence of malformations in human pregnancies has not been established for oxycodone as the data are limited. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss.

No reproductive or developmental studies were conducted with the combination of oxycodone and APAP, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum recommended human dose (MRHD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MRHD. In mice treated with acetaminophen at doses within the clinical dosing range, a reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation. Reproductive studies in rats and rabbits with doses of oxycodone greater than clinical doses did not show any teratogenic or embryo-fetal toxic effects. XARTEMIS XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged maternal use of Xartemis XR during pregnancy can result in withdrawal signs in the neonate. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly.

Use of XartemisXR during pregnancy can result in respiratory depression in the neonate. Observe the neonate for signs of respiratory depression.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. XARTEMIS XR is not recommended for use in women during or immediately prior to labor. Neonates whose mothers received opioid analgesics during labor, must be observed closely for signs of respiratory depression. An specific narcotic opioid antagonist such as naloxone must be available for reversal of narcotic-opioid induced respiratory depression in the neonate.

Data

Human Data

Two large population based studies have evaluated the safety of acetaminophen in pregnant women during the first trimester; neither study showed an increased risk of developing fetal abnormalities.

Available published data on oxycodone exposure during pregnancy and risk for birth defects are limited and do not allow conclusions regarding a possible association.

Animal Data

No reproductive or developmental studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.

Pregnant rats that received oral acetaminophen during days 8 to 14 of gestation at doses up to 350 mg/kg (approximately 0.9 times the maximum human daily dose (MHDD) of 4 grams/day based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison. In a continuous breeding study for the National Toxicology Program, pregnant Swiss CD-1 mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups. Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times

the daily oral dose of 90 mg for adults based on a body surface area comparison) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg based on body surface area comparison), it was non teratogenic or embryo-fetal toxic.

8.3 Nursing Mothers

Oxycodone is present in human milk and may result in accumulation and toxicities such as sedation and respiratory depression in some infants. There is one well-documented report of opioid intoxication in a breast-fed infant that resolved when the infant was administered naloxone. Acetaminophen is present in human milk in small quantities. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Because of the potential for serious adverse reactions in nursing infants from XARTEMIS XR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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/s/

LEYLA SAHIN

10/28/2013

JEANINE A BEST

10/29/2013

LYNNE P YAO

10/30/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Pediatric Labeling Review

Date: October 21, 2013

From: Erica Radden, M.D., Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Drug: Xartemis XR (oxycodone hydrochloride/acetaminophen)

NDA number: NDA 204031

Sponsor: Mallinckrodt Pharmaceuticals, Inc.

Subject: Pediatric Use Labeling

Consult question: Division requests input/guidance regarding labeling.

Materials Reviewed:

- Proposed sponsor labeling for Xartemis XR (oxycodone HCl/acetaminophen) (August 23, 2013)
- Deferral Request for Pediatric Studies, NDA 204-031 (May 28, 2013)
- Cover Letter for Amended Request for Proprietary Name Review, NDA 204-031 (August 23, 2013)

BACKGROUND

Xartemis XR (oxycodone hydrochloride/acetaminophen) Extended-Release Tablet is a combination analgesic consisting of an oral opioid and a non-opioid, non-salicylic acid product formulated for both immediate-release (IR) and extended-release (ER) in a gastroretentive drug delivery system. The NDA for Xartemis XR was submitted on May 24, 2013, with the proposed indication for management of (b) (4) acute pain. The Pediatric Research and Equity Act (PREA) was triggered for the new dosing regimen [2 tablets every 12 hours for Xartemis XR vs. 1 tablet every 6 hours for Percocet (IR oxycodone/acetaminophen)]. FDA advised the sponsor in the pre-NDA meeting (January 7, 2013) that because this indication (i.e., for treatment of acute pain) is applicable to the entire pediatric population, pharmacokinetics (PK) and safety must be assessed over the entire pediatric age range, and efficacy must be assessed for pediatric patients under the age of 2 years. DAAAP has determined that efficacy can be extrapolated from adequate and well controlled studies in adults down to 2 years of age. Therefore, the sponsor is requesting a deferral of pediatric studies for all pediatric age groups based on criteria that the drug is ready for approval for use in adults before pediatric studies are complete. The sponsor plans to complete studies sequentially in adolescent patients (12-17 years of age) first, and proceed to children (2-11 years of age) and then patients less than 2 years of age. The sponsor will develop an age-appropriate formulation for patients less than 12 years of age.

Of note, PREA postmarketing requirements (PMRs) are outstanding for three oxycodone formulations (oxycodone HCl 5 mg capsules, oxycodone HCl 100 mg/5 mL oral solution and oxycodone HCl 5 mg/5 mL oral solution). Each product has the same PREA PMRs; 1) to conduct a pharmacokinetic (PK), safety and efficacy study in patients birth to 2 years of age and 2) a PK and safety study in patients >2 years to <17 years of age. There is also an outstanding PREA PMR for Ofirmev (acetaminophen for injection) to conduct a randomized, double-blind, adequately controlled study of efficacy, pharmacokinetics and pharmacodynamics of intravenous (IV) acetaminophen (APAP) for the treatment of acute pain in pediatric patients from 0 to 2 years of age.

Reviewer comment: The findings from these existing PREA PMRs may impact the study design and safety monitoring for the Xartemis XR PMR. If possible, based on public availability of the data and right of reference, all available information should be leveraged. For this reason, the Xartemis XR PMR should be written in general terms (e.g., without outlining very specific study requirements that might preclude leveraging available data).

(b) (4)

The Division has requested PMHS' input regarding appropriate labeling for the pediatric population.

PROPOSED SPONSOR LABELING (Submitted May 28, 2013)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under the age of 18 have not been established.

Discussion on Labeling Recommendations

If a deferral of studies for the entire pediatric age range is granted, the currently proposed language for the Pediatric Use subsection is appropriate because Xartemis XR has not been studied in pediatric patients and is not approved for use in the pediatric population. However, PMHS recommends including the drug name in the pediatric use statement. Furthermore, the Labeling Review Tool on the Study Endpoints and Labeling Development webpage recommends that the absence of information about the safety and effectiveness of a drug in a specific population (e.g., children) should not be included under the Highlights section. (b) (4)

Additionally, similar to labeling for Oxycodone HCL Controlled-Release Tablets, PMHS recommends that DAAAP consider adding a statement that Xartemis XR Extended-Release Tablets cannot be crushed or divided for administration, if applicable.

The Warnings and Precautions section of labeling should include the safety concern related to serious skin reactions with acetaminophen use. A Drug Safety Communication was issued August 1, 2013, that acetaminophen has been associated with risk of rare but potentially fatal skin reactions known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).¹

Proposed labeling in the Warnings and Precautions section includes the safety concern for hepatotoxicity with acetaminophen use. However, safety concerns regarding an association of hepatotoxicity and chronic acetaminophen exposure specifically in pediatric patients have been reported. These cases of acute liver failure have occurred in

¹

<http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm363519.htm>

patients taking recommended dosages of acetaminophen (10-15 mg/kg, ≤ 5 doses/day, maximum 75 mg/kg/day).² The significance of this risk and need to update acetaminophen labeling is currently being considered, particularly with regards to the Dosage and Administration and Warnings and Precautions sections of labeling. Therefore, given the extended-release delivery of this acetaminophen-containing product and potential increased risk of acetaminophen hepatotoxicity in pediatric patients, PMHS recommends that DAAAP consider whether the risk of liver failure should also be incorporated into Xartemis XR labeling, even if not specifically approved for use in children. In addition to including information on this risk in the Warnings and Precautions section and Pediatric Use section for Xartemis XR, DAAAP should consider clarifying in the Indications and Usage section that Xartemis XR is approved for treatment in adults only. These recommendations appear consistent with guidance under development by the Office of Medical Policy. Therefore, PMHS recommends that if there is a known safety concern in the pediatric population and the product is not approved for use in pediatric patients, the indication statement should be written to reflect approval only in adults. In addition, if the concern does not warrant a contraindication, the Indications and Usage section may also include a limitation of use statement about the significant risk in the pediatric population. A cross-reference should be included to the section of labeling where this detailed information can be found [e.g., Warnings and Precautions- Hepatotoxicity (5.X) and Use In Specific Populations- Pediatric Use (8.4)].

PMHS LABELING RECOMMENDATIONS:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of Xartemis XR in pediatric patients under the age of 18 years have not been established.

PMHS Involvement:

PMHS participated in team and labeling meetings held between August, 2013 and October, 2013. Our input will be reflected in the final labeling. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

² Leonis MA, Alonso EM, Im K, Belle SH, Squires RH and for the Pediatric Acute Liver Failure Study Group. Chronic Acetaminophen Exposure in Pediatric Acute Liver Failure. *Pediatrics* March 2013;131(3):e740-e746.

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/s/

ERICA D RADDEN
10/21/2013

HARI C SACHS
10/21/2013
I agree with these recommendations.

LYNNE P YAO
10/24/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: October 17, 2013

TO: Dominic Chiapperino, Ph.D., Regulatory Project Manager
Elizabeth Kilgore, M.D., Clinical Reviewer
Ellen Fields, M.D., Clinical Team Leader
Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (OSI)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (OSI)

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-031

APPLICANT: Mallinckrodt, Inc.

DRUG: Xartemis[®] (oxycodone and acetaminophen)

NME: No

INDICATION: Management of (b) (4) acute pain

THERAPEUTIC CLASSIFICATION: Priority

CONSULTATION REQUEST DATE: July 3, 2013

INSPECTION SUMMARY GOAL DATE: October 24, 2013

REVIEW DIVISION ACTION GOAL DATE: November 22, 2013

PDUFA DUE DATE: November 28, 2013

I. BACKGROUND

This NDA for the combination analgesic oxycodone hydrochloride (**OC**) and acetaminophen (**APAP**) was submitted as a 505(b)(2) application for priority review for the indication of (b) (4) acute pain, (b) (4). The OC-APAP product was developed under the name COV795 with the proposed trade name Xartemis® (pending approval).

Relief from acute post-surgical pain requires immediate-release agents effective within one hour of administration. The compounds used for acute pain are typically short-acting (rapidly absorbed and eliminated), and therefore require frequent (inconvenient) administration. COV795 was formulated as an oral (b) (4)-release tablet with multiple layers of two well known active ingredients, OC and APAP, for their rapid and sustained therapeutic plasma levels. OC is a semi-synthetic opioid agonist analgesic with anxiolytic effects (euphoria and relaxation), respiratory depression, and cough reflex suppression. APAP is a non-opiate, non-salicylate analgesic and antipyretic. COV795 consists of a fixed combination of 7.5 mg OC and 325 mg APAP formulated for optimal analgesia and safety (acetaminophen hepatotoxicity). The application was accepted under 505(b)(2) based on the similarity of the active ingredients with those previously found to be safe and effective (listed drugs Roxicodone® and Ultracet®). Priority review was granted based on (new) claims of product abuse deterrence, presumably from product formulation using gastro-retentive technology ((b) (4) release of the active agents with similar dissolution in water, gastric fluid, or alcohol). The following two original studies were performed (and audited) in support of this priority 505(b)(2) NDA.

COV15000181 (Study 181): *An Open-Label Safety Study of COV795 in Subjects with Osteoarthritis or Chronic Low Back Pain*

This study was conducted over nine months (from September 2011 to June 2012) as a multicenter, open-label study in 376 subjects (safety population) with osteoarthritis (**OA**) of the hip or knee or chronic low back pain (**CLBP**) transitioning from Step 1 (no opioid) to Step 2 (opioid requirement) of the World Health Organization (**WHO**) pain scales.

The primary study objective was to demonstrate the safety and tolerability of COV795 after up to 35 days of use by physical examination, vital signs, pulse oximetry, laboratory tests, and clinical AE monitoring. Study enrollment was discontinued when ≥ 250 subjects were exposed to COV795 for ≥ 10 days, oral dosing of two tablets every 12 hours (**Q12h**).

• Subject Selection

- Men or women (≥ 18 years of age) with OA of the knee or hip or moderate to severe CLBP
- Numerical Rating Scale (**NRS**) pain score ≥ 3 (Visit 1) and ≥ 4 (Visit 2) for the last 24 hours
- Exclusion: surgery of OA study joint or for CLBP within six months

• Treatment Regimen

- Open-label COV795, two tablets orally Q12h for up to 35 days
- Follow-up phone call at Day 43 \pm 2 days

• Study Evaluations

- Co-primary endpoints for safety: time to treatment discontinuation; changes in physical findings, vital signs, and pulse oximetry; clinical laboratory tests (including liver function tests); clinical adverse events (**AEs**)
- Major secondary endpoints for efficacy (screening visit, Visit 2, and Visits 4 - 8): changes from pre-treatment in the last 24 hours (worst, least, and average pain) and currently (pain, pain relief, and pain-related quality of life, **QoL**), as assessed using the following questionnaires:
 - *Modified Brief Pain Inventory Short Form (mBPI-sf)*: pain (questions 1-4), pain relief (question 5), and pain-related QoL (pain interference subscale)

- Change in disease-specific QoL: (1) *Western Ontario and McMaster Universities Arthritis (WOMAC)* 48-hour version for hip/knee osteoarthritis, and (2) *Roland Morris Low Back Pain and Disability (RM-LBPD)*

- **Major Findings**

- Scores for worst, least, average, and current pain all decreased over the course of the study. The improvements in pain scores occurred early and persisted.
- 91 subjects (24.2%) discontinued the study early. The mean time to discontinuation was 7.7 days (73 subjects after an AE). Four serious AEs were observed in four subjects, including two deaths (respiratory arrest and traffic accident).
- Serious AEs (SAEs): moderate abdominal pain (one subject, considered treatment-related) and atrial fibrillation (one subject, considered not treatment-related)
- 235 subjects (63%) had at least one AE, of which about one-half were considered treatment-related. Nausea (typically mild or moderate) was the most common AE considered treatment-related (23% of subjects).
- Changes in laboratory results, vital signs, pulse oximetry, and physical findings were small and did not appear clinically significant. Five subjects were discontinued from study drug due to elevated liver enzymes (uneventful resolution after study drug discontinuation).

COV15000182 (Study 182): *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 Postoperative Bunionectomy Pain Followed by an Open-Label Extension*

This study was conducted over nine months (from November 2011 to August 2012) as a multi-center, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study in 329 subjects (safety population) to evaluate the efficacy and safety of COV795 in managing acute post-surgical pain following simple unilateral bunionectomy.

The primary study objective was to demonstrate the analgesic efficacy of COV795 against placebo using summed pain intensity difference (SPID) over the first 48 hours (SPID-48). Cohort 1 consisted of subjects enrolled before Amendment 2; these subjects were given a single dose (then Q12h if repeat doses were requested). Cohort 2 consisted of those enrolled at or after Amendment 2; these subjects started with Q12h dosing.

- **Subject Selection**

- Men or women (age 18 - 75 years) in good general health, scheduled for primary unilateral first metatarsal bunionectomy
- Physical Status Classification of PS-1 or PS-2 (American Society of Anesthetists): Postoperative pain score of ≥ 4 between one and 9 hours after discontinuation of nerve block and ≥ 30 minutes after removing ice pack
- Exclusion: severe bronchial asthma, hypercarbia, or hypoxia within the last 10 years, glycosylated hemoglobin $> 7\%$

- **Treatment Groups and Regimen**

- COV795: fixed combination of 7.5 mg OC and 325 mg APAP
- COV795 or matching placebo, two tablets Q12h orally for two days, follow-up for 7 ± 2 days
- Optional open-label dosing for up to 14 days after blinded dosing, phone follow-up in 7 ± 2 days

• Study Evaluations

- Primary endpoint: SPID-48
- Major secondary endpoints: times to meaningful pain relief and peak PID
- Safety: physical exam, cardiogram, laboratory, and AE monitoring

Endpoint Definitions

- Time to confirmed perceptible pain relief: minutes to meaningful pain relief (no rescue medication) within four hours of initial dosing
- SPID: sum of time-weighted PID scores (from pre-dose baseline score)
- Sum of the time-weighted total pain relief scores (TOTPAR): sum of time-weighted total pain relief scores at each time point over a period of time
- Responders: subjects with $\geq 30\%$ reduction in pain intensity score at time of interest without rescue medication
- Mean dosing interval: minutes between doses of interest; if rescue medication used (any dose during blinded phase), minutes after dosing to rescue medication use

• Major Findings

- Subjects given COV795 reported less pain than those given placebo.
- Mean SPID-48 was significantly greater for COV795 than for placebo (115 vs 67, $p < 0.001$).
- Greater PID for COV795 than for placebo after each dose of study drug.
- Four subjects reported a total of four serious AEs (no deaths).
- Nausea was the most common AE (31% COV795, 6% placebo).

II. CLINICAL INSPECTIONS

Two pivotal studies were audited at good clinical practice (GCP) inspections at 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.

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. Pasadena, 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)

Pending: The final establishment inspection report (EIR) has not been received from the field office and OSI's final review and classification of the inspection outcome remains pending.

1. Samir J. Azzam, M.D.**a. What was inspected: Audit of Study 181**

- General compliance review
 - Study protocol, standard operating procedures (**SOPs**), GCP regulations
 - Subject eligibility, informed consent, subject randomization
 - Study blind, protocol violations, subject discontinuations
 - Test article disposition and accountability, investigator financial disclosures
 - Study monitoring, institutional review board (**IRB**) oversight
- Verification of major endpoint data
 - Primary endpoint (safety): time to treatment discontinuation
 - Major secondary endpoints (safety): clinical AEs and liver function tests
 - Secondary endpoint (efficacy): change in pain (last 24 hours, from pre-treatment) as assessed using mBPI-sf and either WOMAC or RM-LBP
- Subject disposition and records review:
 - Study 181 at Site 166: 46 subjects were screened, 27 were enrolled (and dosed), and 25 completed the study.
 - Case records were reviewed completely for 15 enrolled subjects (56%) and partially for the remaining 12 subjects. Study data were verified for the primary endpoint, major secondary endpoints, and AEs.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor deficiencies were verbally discussed (not cited, inspector discretion):
 - For one subject, one incidence of dizziness (documented in progress notes) was not reported to the sponsor (apparent isolated oversight).
 - One subject was enrolled and dosed before all screening laboratory results were received (subject eligibility later confirmed).

The observed deficiencies (verbally discussed) appear minor and isolated, and are not expected to impact study outcome. Other than as described above:

- Overall study monitoring and oversight by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was adequately documented. Underreporting of AEs was not observed.
- Source records and case report forms (**CRFs**) appeared complete.
- Audited endpoint data matched among source records, CRFs, and NDA listings.

c. Assessment of data integrity: Data from this study site appear reliable.**2. Sonia Singla, M.D.****a. What was inspected: Audit of Study 182**

- General compliance review
 - Study protocol, GCP regulations
 - Subject eligibility, informed consent, subject randomization
 - Study blind, protocol violations, subject discontinuations
 - Test article accountability, investigator financial disclosures, study monitoring

- Verification of major endpoint data
 - Efficacy (primary endpoint): numerical rating on NRS (raw data for calculating PID)
 - Safety: SAEs
- Subject disposition and records review:
 - Study 182 at Site 001: 182 subjects were screened, 89 were randomized (and dosed), and 77 completed the study (48 also completed open-label extension).
 - Case records were reviewed completely for 15 enrolled subjects (17%) and partially for 38 of the remaining 74 enrolled subjects (partial or complete for 60% of enrolled), to include verification of the major study data.
- b. General observations and comments:
 - No significant deficiencies were observed and a Form FDA483 was not issued. The following minor deficiencies were verbally discussed (not cited, inspector discretion):
 - For one subject, one incidence of neck and shoulder pain was not reported to the sponsor (apparent isolated oversight).
 - Minor data entry errors and protocol deviations (including minor irregularities in drug accountability) confirmed as listed in the NDA listings

The observed deficiencies (verbally discussed) appear minor and isolated, and are not expected to impact study outcome. Other than as described above:

- Overall study monitoring and oversight by the sponsor and IRB appeared adequate.
 - All subjects signed the informed consent document.
 - Drug accountability was adequately documented. Underreporting of AEs was not observed.
 - Audited endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communications with the field investigator. The final establishment inspection report (**EIR**) has not been received from the field office and OSI's final review and classification of the inspection outcome remains pending.

3. Richard A. Pollak, M.D.

- a. What was inspected: Audit of Study 182
- General compliance review
 - Study protocol, GCP regulations
 - Subject eligibility, informed consent, protocol violations, subject discontinuations
 - Investigator financial disclosures
 - Verification of major endpoint data
 - Efficacy: SPID-48, minutes to meaningful pain relief, and peak PID
 - Safety: AEs and laboratory tests
 - Subject disposition and records review:
 - Study 182 at Site 203: 151 subjects were screened, 83 were enrolled, and 82 completed the study.
 - Case records were reviewed completely for 23 enrolled subjects (28%), to include verification of the major study data.

b. General observations and comments:

- No deficiencies were observed and a Form FDA483 was not issued.
- Overall study monitoring and oversight by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was well documented. Underreporting of AEs was not observed.
- Source records and CRFs appeared complete.
- Audited endpoint data matched among source records, CRFs, and NDA listings.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communications with the field investigator. The final EIR has not been received from the field office and OSI's final review and classification of the inspection outcome remains pending.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

This NDA for oxycodone hydrochloride and acetaminophen ((b)(4))-release tablet, proposed name *Xartemis*[®]) was accepted for priority review based on new claims of abuse deterrence when used for (b)(4) acute pain. For this 505(b)(2) application, the safety and efficacy of the combination product are supported by the similarity of the active ingredients with previously approved agents (listed drugs Roxicodone[®] and Ultracet[®]). Original data were also obtained in new clinical studies. Study 182 was a randomized controlled study in subjects with postoperative (bunionectomy) pain. Study 181 was an open-label safety study in subjects with osteoarthritis or chronic low back pain.

Two studies were audited at three GCP inspections, at one (clinical study) site in Study 181 and at two sites in Study 182. The three sites were selected for their relatively large subject enrollment in their respective study. Abuse deterrence was not formally evaluated in either study; supporting data were obtained in studies not audited at pre-approval GCP inspections. At all three sites, no significant GCP deficiencies were observed and a Form FDA 483 was not issued. Deficiency observations were limited to minor and/or isolated findings. The study data from all three sites for Studies 181 and 182 appear reliable as reported in the NDA.

Note: For two Sites 001 (Singla) and 203 (Pollak) in Study 182, the EIR has not been received from the field office and the outcome classification remains pending. The observations noted above are based on preliminary communication with the field investigator. An addendum to this inspection summary will be forwarded to DAAAP if the outcome classification changes or if additional observations of clinical or regulatory significance are discovered after receipt and review of the final EIRs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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/s/

JONG HOON LEE
10/17/2013

JANICE K POHLMAN
10/17/2013

KASSA AYALEW
10/17/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 11, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Xartemis XR (Oxycodone Hydrochloride and
Acetaminophen Extended Release Tablets) 7.5 mg/325 mg

Application Type/Number: NDA 204031

Applicant: Mallinckrodt Inc.

OSE RCM #: 2013-1271

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION AND REGULATORY HISTORY

This review evaluates the proposed bottle and blister container labels, and insert and blister carton labeling for Xartemis XR submitted on August 23, 2013, for design elements that could lead to medication errors.

On May 28, 2013, Mallinckrodt Inc. submitted NDA 204031 for Xartemis XR (oxycodone hydrochloride and acetaminophen extended release tablets), 7.5 mg/325 mg for the management of (b) (4) acute pain.

1.1 PRODUCT INFORMATION

The following product information is provided in the insert labeling submitted August 23, 2013:

- Established name: Oxycodone hydrochloride and Acetaminophen extended release tablets
- Indication of Use: the management of (b) (4) acute pain
- Route of administration: oral
- Dosage Form: extended release tablet
- Strength: fixed dose combination 7.5 mg OC/325 mg APAP
- Dose: two tablets every 12 hours (maximum 4 tablets or 30 mg/1300 mg daily)
- How Supplied and Container/Closure System: 100 tablets/bottle and 10 tablets per blister card; 10 cards per carton; 100 tablets/carton
- Storage: 25°C (77°F)
- Applicant: Mallinckrodt Inc.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) uses the principles of human factors and Failure Mode and Effects Analysis,¹ to identify potential sources of errors with proposed bottle and unit dose blister container labels, and insert and unit dose blister carton labeling. DMEPA evaluated the following:

- Proposed Unit Dose Blister and Bottle Container Labels submitted August 23, 2013 (Appendix A)
- Proposed Unit Dose Carton Labeling submitted August 23, 2013 (Appendix B)
- Insert Labeling submitted August 23, 2013

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

In the December 13, 2012, Pre-NDA meeting, DMEPA recommended that the Applicant use educational, label and labeling strategies to avert potential confusion between the oxycodone/acetaminophen (OC/APAP) immediate release products and Xartemis XR. Both products share a common strength of 7.5 mg OC/325 mg APAP.

Xartemis XR should not be cut, crushed, split, or chewed unlike the OC/APAP immediate release products. We note that the proposed bottle container labels and unit dose blister carton labeling includes the statement on the principal display panel “(b) (4)” which may help mitigate medication errors related to wrong technique with this extended release product.

Furthermore, Xartemis XR is dosed at a frequency of every 12 hours whereas OC/APAP immediate release products are primarily dosed every 4 to 6 hours. Therefore, DMEPA recommends that the applicant use a label and labeling error mitigation strategy similar to that used in other extended-release products which have immediate-release counterparts, such as extended and immediate release hydromorphone. Xartemis XR has a fixed-dosing interval and the addition of dosing instructions on the principal display panel alerts practitioners to the frequency of administration which may mitigate wrong frequency errors, if they were to occur.

The unit dose blister container and carton labeling do not display the milligram amount of drug per single unit in a manner that mitigates confusion as to how much product is contained in a single unit compared to the total contents of the entire blister card.

See our recommendations in Section 5.

4 CONCLUSIONS

DMEPA concludes that the proposed container label and blister and carton labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. We request the recommendations for the container labels in Section 5 be communicated to the Applicant prior to approval.

5 RECOMMENDATIONS

DMEPA recommends that following be implemented prior to approval of the application:

- A. All Container Labels (Bottle and Unit Dose) and Carton Labeling
 1. Revise the presentation of the proprietary name so it appears in title case rather than all capital letters to improve readability.
 2. Remove the intervening graphic, which extends from the first letter “X” and above the proprietary name, to improve readability.
 3. Revise the established name to include the dosage form “oxycodone hydrochloride/acetaminophen extended release tablets”.
 4. Revise the font color of the strength statement from (b) (4) to improve readability. As presented, the light colored font on a light colored background may be difficult to read.

B. Bottle Container Labels and Carton Labeling

1. Ensure there is adequate white space between the established name and the CII designation so that the CII designation does not interfere with the readability or appear as a part of the established name statement.
2. Realign the strength statement so that its justification is aligned to the left to allow space for the next recommendation.
3. Consider adding the following dosing instruction statement to appear after the strength statement and on a separate line: “every 12 hours” as a label and labeling strategy to alert practitioners of the frequency of administration.
4. Revise the statement from “(b) (4)” to read “Swallow whole. Do Not break, chew, crush, cut, dissolve, or split Xartemis XR”

C. Unit Dose Blister Labels

1. Reduce the size of the CII designation, as presented it is more prominent than and may distract from other important information, such as the proprietary and established names.
2. If space permits, revise the appearance of strength on the blister container backing to describe the milligram amount of drug per single unit to appear as follows:

XX mg/XX mg per tablet

D. Unit Dose carton Labeling

1. Revise the appearance of the strength statement on principal display panel of the carton labeling to describe the milligram amount of drug per single unit to mitigate medication errors of wrong dose and to appear as follows:

Contents: XX mg/XX mg per tablet

100 Unit-Dose tablets

If you have further questions or need clarifications, please contact Vaishali Jarral, project manager, at 301-796-4248.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BRENDA V BORDERS-HEMPHILL
10/11/2013

JAMIE C WILKINS PARKER
10/11/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204031	NDA Supplement #: N/A	Efficacy Supplement Type: N/A
Proprietary Name: Xartemis Established/Proper Name: oxycodone hydrochloride and acetaminophen Dosage Form: extended-release tablets Strengths: 7.5 mg/ 325 mg		
Applicant: Mallinckrodt Inc., Hazelwood, MO Agent for Applicant (if applicable): N/A		
Date of Application: May 24, 2013 Date of Receipt: May 28, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: November 28, 2013		Action Goal Date (if different): November 26, 2013
Filing Date: July 27, 2013		Date of Filing Meeting: June 24, 2013
Chemical Classification: Type 3- New Dosage Form		
Proposed indication(s)/Proposed change(s): Management of (b) (4) acute pain where the use of an opioid analgesic is appropriate		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) </div> <div> <input type="checkbox"/> 505(b)(1) N/A <input type="checkbox"/> 505(b)(2) </div> </div>	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority </div> <div> <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted </div> </div>	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<div style="display: flex; flex-direction: column;"> <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) </div>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): INDs 104702 (main development program) and 109246				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	X			
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	X			
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm	X			
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				N/A
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				N/A
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			X		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?			X		
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>			X		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes , # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)	X			
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: 5/29/13</i></p>	X			
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i></p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	X			
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X			
<i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only):				
Is this submission a complete response to a pediatric Written Request?		X		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	X			OSE consult sent
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				

Other Consults	YES	NO	NA	Comment
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4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			PMHS, for section 8 Use in Specific Populations, package insert, 8-22-13
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 12/7/2011	X			Written responses to pre-Phase 3 questions
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 1/7/2013	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 24, 2013

BLA/NDA/Supp #: NDA 204031

PROPRIETARY NAME: Xartemis XR

ESTABLISHED/PROPER NAME: oxycodone hydrochloride and acetaminophen

DOSAGE FORM/STRENGTH: extended-release tablets

APPLICANT: Mallinckrodt Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for management of (b) (4) pain where use of an opioid analgesic is appropriate

BACKGROUND: The proposed product is formulated with physiochemical characteristics intended to deter abuse, and these properties have been investigated through in vitro and clinical studies. The NDA is submitted via the 505(b)(2) regulatory pathway with reference to listed products, Roxicodone® (15 mg OC oral tablets, NDA 021011; Mallinckrodt) for the oxycodone drug moiety and Ultracet® (325 mg acetaminophen/37.5 mg tramadol hydrochloride oral tablets, NDA 021123; Janssen Pharms) for acetaminophen drug moiety.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dominic Chiapperino	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Elizabeth Kilgore	Y
	TL:	Ellen Fields	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Feng Li	Y
	TL:	Janice Derr	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Yong Hu	Y
	TL:	Julia Pinto	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	John Metcalfe	Y
	TL:	Stephen Langille	Y
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Juandria Williams	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Vicky Borders-Hemphill	Y
	TL:	Jamie Wilkins Parker	Y
OSE/DRISK (REMS)	Reviewer:	Danielle Smith	Y
	TL:	Reema Mehta	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	John Lee	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewers:	Jim Tolliver	Y
	TL:	Silvia Calderon	Y
Biopharmaceutics	Reviewers:	Kareen Riviere	Y
	TL:	Angelica Dorantes	Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? <div> <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO </div> Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <div> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO </div> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>		BA studies
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? If no, explain: 		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments List comments: No issues 		<input type="checkbox"/> Not Applicable
CLINICAL Comments: none		<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: No new issues needing AC, and not an NME</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments: The submission does not appear to include subgroup analyses by age, gender, or race for your efficacy Study COV15000182US.</p>	<input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. The drug product release specifications currently do not include testing, in accordance with USP 1217, for tablet hardness. 2. The submission currently does not appear to address whether or how large the intact tablet will swell and whether it becomes sticky in water and in simulated gastric fluids over time. This information may help assess the risk of GI obstruction due to the tablet. 3. The submission currently does not contain adequate data to characterize the dissolution profile of the drug product in order to support the selection of the proposed dissolution acceptance criteria (i.e., specification-sampling time points and values) for your proposed drug product specifications. 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<input type="checkbox"/> Not Applicable
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Bob A. Rappaport, MD, Division Director, DAAAP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Aug. 29, 2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <ul style="list-style-type: none"> ■ Mid-Cycle Meeting: Aug. 29th ■ Wrap-Up Meeting: Oct. 24th ■ Primary reviews: by Nov. 1st ■ Secondary/TL memos: by Nov. 7th ■ Labeling to sponsor, PMRs, REMS: by Nov. 12th ■ CDTL memo: Nov. 13th ■ Exec Memo/Action: Nov. 28th (or sooner) 	

Comments: none	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:

	http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204031

Application Type: New NDA

Name of Drug: Xartemis (oxycodone hydrochloride/acetaminophen) (b) (4)-release tablets, 7.5 mg/325 mg

Applicant: Mallinckrodt Inc.

Submission Date: May 24, 2013

Receipt Date: May 28, 2013

1.0 Regulatory History and Applicant's Main Proposals

NDA 204031 provides for a new formulation of the oxycodone/acetaminophen which differs from already-approved similar formulations of this combination and strength in that it proposed product purports to have abuse-deterrent features. The NDA submission is consistent with advice from DAAAP from an End-of-Phase 1 advice letter (Meeting – Written Responses), dated December 7, 2011, and the meeting minutes dated January 7, 2013 from the Pre-NDA meeting held December 13, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 15, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Acceptable*

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The length of HL does exceed the ½ page limit. However, all products in this class require text in excess of a ½ page to convey necessary information in HL. This need not be conveyed as deficiency in the 74-day letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Acceptable*

- NO** 4. White space must be present before each major heading in HL.

Comment: *Some headings do not have any white space to separate them from preceding paragraphs.*

Selected Requirements of Prescribing Information (SRPI)

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Acceptable*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *Acceptable*

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *Acceptable*

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment: *Acceptable*

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *Acceptable*

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment: *Acceptable*

Selected Requirements of Prescribing Information (SRPI)

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Acceptable*

Boxed Warning

- NO** 12. All text must be **bolded**.

Comment: *The list of specific warnings is not in bold font.*

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment: *Acceptable*

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment: *Acceptable*

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment: *Acceptable*

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment: *Acceptable*

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: *The indication statement should be revised to include the pharmacologic class, opioid agonist, for oxycodone.*

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.
- **Comment:** *The following text needs to be corrected such that “mg” is appropriately placed: “(b) (4) -release tablets (oxycodone/acetaminophen mg): 7.5/325 (3.)” However, this is more a content issue than format and need not be included in the 74-day letter.*

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.
- Comment:** *Acceptable*
- YES** 24. Each contraindication is bulleted when there is more than one contraindication.
- Comment:** *Acceptable*

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.
- Comment:** *Acceptable*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):
- If a product **does not** have FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION**”
- If a product **has** FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
 - “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”
- Comment:** *Acceptable*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.
- Comment:** *Acceptable*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
- Comment:** *Acceptable*
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Selected Requirements of Prescribing Information (SRPI)

Comment: *Acceptable*

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Acceptable*

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *The title for the Boxed Warning must be revised to match the title used in the HL Boxed Warning.*

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment: *Acceptable*

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment: *Acceptable*

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment: *Acceptable*

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: *Acceptable*

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment: *Acceptable*

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment: *Acceptable*

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery

Selected Requirements of Prescribing Information (SRPI)

8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Acceptable*

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Acceptable*

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Acceptable*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment: *Acceptable*

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment: *Acceptable*

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment: *Acceptable*

Selected Requirements of Prescribing Information (SRPI)

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment: The statement in the Xartemis label is verbatim, except for use of the word (b) (4) instead of “trial.” It may be that (b) (4) is an appropriate modification and this will be considered a review issue, and not listed as a deficiency in the 74-day letter.

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: Acceptable

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: Acceptable

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

/s/

DOMINIC CHIAPPERINO
08/23/2013