CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205777	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Targiniq ER Established/Proper Name: oxycodone HCL/naloxone HCl Dosage Form: extended-release tablets Strengths: 10/5, 20/10, 40/20 mg/mL		
Applicant: Purdue Pharma L.P.		
Date of Receipt: September 23, 2013		
PDUFA Goal Date: July 23, 2014	Action Goal Date (if different):	
RPM: Lisa Basham		
Proposed Indication(s): management of pain severe enough to require daily, around-the-clock, long-term 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)
NDA 16636 "Narcan"	Labeling, previous finding of safety and efficacy
NDA 22272 "OxyContin"	Labeling, previous finding of safety and efficacy

*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)

Relative BA study to approved NDA product OxyContin (also Purdue's) and Narcan (via an ANDA generic designated as the RLD for Narcan)

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)
OxyContin (belongs to Purdue)	022272 (reformulated) and 020553 (original)	Yes
Narcan	ANDA 016636 (need RLD ANDA #)	Yes

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:

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:

OxyContin original formulation (NDA 020553). Discontinued for reasons of safety (not effectiveness) due to the approval and availability of a safer formulation (more difficult to abuse).

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 application proposes a new combination of previously approved drugs

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 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 ☐

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

N/A ☐ YES ☐ NO ☐

OxyContin belongs to the applicant.

*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):

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):

(Narcan) 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/

LISA E BASHAM
07/23/2014

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/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 205777 for Targiniq ER
PMR/PMC Description:	Conduct one or more studies to provide quantitative estimates of the risks of misuse, abuse, addiction, overdose and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy. These studies should address at a minimum the following specific aims: I. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death. II. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	8/14
	Study/Trial Completion:	01/18
	Final Report Submission:	06/18
	Other: _____	MM/DD/YYYY

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

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

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."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

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 initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, the codes for these outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

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)

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.*

_____

(signature line for BLAs)

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/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 205777 for Targiniq ER
PMR/PMC Description:	Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition) , which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/14
	Study/Trial Completion:	08/15
	Final Report Submission:	11/15
	Other:	MM/DD/YYYY

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

   The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the outcomes need to be validated, including measures of opioid-related adverse events.

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.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of the opioid-related adverse event, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

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)

_____

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.*

_____

(signature line for BLAs)

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/BLA #	ER/LA opioid analgesics, with the addition now of NDA 205777 for Targiniq
Product Name:	ER

PMR/PMC Description: Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/14
	Study/Trial Completion:	08/15
	Final Report Submission:	11/15
	Other:	MM/DD/YYYY

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

   The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events: misuse, abuse, addiction, overdose, and death need to be validated.

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.

An observational study would likely be conducted that includes identifying patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse abuse, addiction, overdose, and death, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition.

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)

_____

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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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/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 205777 for Targiniq ER
PMR/PMC Description:	Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse, and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/14
	Study/Trial Completion:	08/15
	Final Report Submission:	11/15
	Other:	MM/DD/YYYY

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

   The data needed to validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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."

   A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

   In order to conduct such a study, the outcomes need to be validated, including measures of "doctor/pharmacy shopping" which are suggestive of misuse, abuse, and/or addiction.

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.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of "doctor/pharmacy shopping", and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

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)

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

_____

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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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/BLA # ER/LA opioid analgesics, with the addition now of NDA 205777 for Targiniq
Product Name: ER

PMR/PMC Description: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/14
	Study/Trial Completion:	08/16
	Final Report Submission:	02/17
	Other:	MM/DD/YYYY

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

   In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

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."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.

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.

A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

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)

_____

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/

MARK A LIBERATORE
07/23/2014

JUDITH A RACOOSIN
07/23/2014

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/BLA # NDA 205777
Product Name: TARGINIQ ER

PMR/PMC Description: Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	12/31/2014
Study/Trial Completion:	12/31/2018
Final Report Submission:	06/30/2019
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 the required pediatric study for this application because this product is ready for approval for use in adults and the pediatric study has not been started.

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 TARGINIQ ER in pediatric patients ages (b) (4) to less than 17 years old.

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 TARGINIQ ER in patients ages (b) (4) to less than 17 years old.

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)
☐ 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

Continuation of Question 4

☐ 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)
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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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/

MARK A LIBERATORE
07/23/2014

JUDITH A RACOOSIN
07/23/2014

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/BLA # 205777
Product Name:

PMR/PMC Description: A postmarketing observational cohort study comparing Targiniq ER to other drugs approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The study's outcome is serious cardiovascular thromboembolic events; a concise case definition should be provided. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Targiniq ER-exposed patients. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in serious cardiovascular thromboembolic risk above the comparator background rate, using a pre-specified statistical analysis method. For the Targiniq ER-exposed and comparator(s)-exposed patients, the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least six months of Targiniq ER exposure at the end of the study.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	4/2015
	Study/Trial Completion:	4/2019
	Final Report Submission:	11/2019
	Other:	MM/DD/YYYY

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

A substantial amount of drug exposure in the general population is needed to conduct this study given the expectation of a relatively low incidence of the outcome.

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."

On June 11-12, 2014, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss the potential cardiovascular risk associated with products in the class of peripherally-acting mu opioid receptor antagonists (PAMORAs). AADPAC generally agreed that controlled cardiac outcome trials are not needed for this class of drugs intended to treat OIC, due to lack of a clear cardiac signal during development programs. Some members of the panel thought that it may be reassuring to collect post marketing data on cardiac safety via observational studies in order to rule out a large increase in MACE (major adverse cardiovascular events) risk. Therefore, as per the recommendation of the AADPAC, and to maintain consistency within this class of opioid antagonists, a post marketing requirement will be imposed on the Applicant such that they must conduct an observational study or studies to further assess the risk of major cardiac adverse events in patients treated with TARGINIQ ER.

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.

A postmarketing observational cohort study comparing Targiniq ER to other drugs approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate with a study outcome of serious cardiovascular thromboembolic events.

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)
☐ 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

Continuation of Question 4

☐ 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)

_____

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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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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/

JUDITH A RACOOSIN
07/23/2014

PMR/PMC Development Template

NDA 205777

PMR/PMC Description: Conduct a combination in vivo micronucleus and comet assay for (b) (4) (b) (4). The comet assay portion of the study should include assessment of both stomach and liver tissue and include doses of the drug substance that would be obtained at the maximum recommended daily dose of the drug product and result in adequate toxicity to ensure assay validity.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	December 2014
	Study Completion:	April 2015
	Final Report Submission:	September 2015
	Other:	

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

The drug substance impurity (b) (4) has been present in naloxone drug substance for many years. The Agency is aware that that the compound has tested negative in the Ames assay but positive in the in vitro chromosomal aberrations assay. As such, the Agency has historically controlled this impurity at a level of NMT (b) (4)%, in part, based on the relatively low clinical dosing for the FDA-approved drug products that contain naloxone. This drug product will result in a greater exposure to naloxone and therefore, a lower specification of NMT (b) (4) is appropriate as per the 2008 draft FDA guidance document on genotoxic impurities. At this time, the impurity is controlled to as low as technically feasible, therefore, reducing this specification is not deemed an approval issue. However, further qualification data or attempts to reduce the impurity are warranted as a post marketing requirement.

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."

The recommended in vivo genetic toxicology assessments will complete a weight-of-evidence assessment of the genotoxic potential of this impurity. Upon review of the study reports, the Agency will determine if the specifications can be less restrictive or if alterations to the manufacturing process are required to reach the NMT (b) (4) threshold.

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 is a nonclinical in vivo genetic toxicology study with multiple endpoints to minimize animal use.

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)

_____

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/

RICHARD D MELLON
07/23/2014

JUDITH A RACOOSIN
07/23/2014

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/BLA # 205777
Product Name: Targiniq ER (oxycodone/naloxone extended release tablets)

PMR/PMC Description: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride extended release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Targiniq ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	7/2015
	Study/Trial Completion:	7/2019
	Final Report Submission:	1/2020
	Other:	

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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of Targiniq ER actually deter abuse of the product in "real world" use.

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."

FDA has determined that the sponsor must conduct individual post-marketing studies of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of Targiniq ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

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 design of the post-marketing study program for Targiniq ER must incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Targiniq ER. In particular, post-marketing studies for Targiniq must include individual assessments of all possible routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of oxycodone and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

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)
☐ 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

Continuation of Question 4

☐ 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)

_____

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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

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/

JUDITH A RACOOSIN
07/23/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 26, 2014
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 205777
Product Name and Strength:	Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) Extended Release Tablets 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg
Submission Date:	June 23, 2014
Applicant/Sponsor Name:	Purdue Pharma L.P.
OSE RCM #:	2013-2447
DMEPA Primary Reviewer:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

DAAAP requested that we review the revised container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labels are acceptable from a medication error perspective.

[1] Borders-Hemphill V. Label and Labeling Review for Targiniq ER (NDA 205777). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Feb 25. 8 p. OSE RCM No.: 2013-2447.

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/s/

EUNICE H CHUNG-DAVIES
06/26/2014

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:	June 25, 2014
To:	Bob A. Rappaport, MD Director **Division of Anesthesiology, 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:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Eunice Chung-Davies, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII
Application Type/Number:	NDA 205-777
Applicant:	Purdue Pharma L.P.

1 INTRODUCTION

On September 22, 2013, Purdue Pharma L.P. submitted for the Agency's review New Drug Application (NDA) 205-777 for TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) with the proposed indication for [redacted] pain [redacted], around-the-clock [redacted].

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) on October 21, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride 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 TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) MG submitted on September 22, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 17, 2014.
- Draft TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) Prescribing Information (PI) submitted on September 22, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on June 17, 2014.
- Draft TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) Prescribing Information (PI) submitted on September 22, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on June 18, 2014.

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)
- ensured that language and formatting is consistent with extend-release/long-acting (ER/LA) class MGs
- 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/

KAREN M DOWDY
06/25/2014

EUNICE H CHUNG-DAVIES
06/25/2014

BARBARA A FULLER
06/25/2014

LASHAWN M GRIFFITHS
06/25/2014

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

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

Memorandum

Date: June 24, 2014

To: Lisa Basham
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D.
Regulatory Review Officer
Office of Professional Drug Promotion (OPDP)

Subject: NDA 205777
OPDP labeling comments for Targiniq ER™ (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII

In response to DAAAP's October 21, 2013 consult request, OPDP has reviewed the draft Prescribing Information, Medication Guide, and carton and container labeling for TARGINIQ ER™ (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII.

The review of the Prescribing Information (PI) is based on the proposed SCPI obtained from Review Division's N:drive \\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 205777 (Oxy Nal_Purdue)\Labeling\PLEASE USE THIS ONE - WORKING COPY PI & MG 6-18-14.docx on June 18, 2014 per instructions from the DAAAP RPM. Please see the comments on the marked up version attached below.

The review of the carton and container labeling is based on the carton and container labeling obtained from the EDR (submission dated 2/14/14). We do not have any comments on the carton and container labeling at this time.

OPDP Comments on the proposed Medication Guide will be sent in collaboration with comments from the DMPP Patient Labeling Group.

If you have any questions for OPDP, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Enclosure:

Marked up Prescribing Information
Carton and container labeling

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/s/

EUNICE H CHUNG-DAVIES
06/24/2014

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 24, 2014

To: Bob Rappaport, M.D., Director
Division of Analgesia, Anesthesia, 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 205-777, Targiniq (Oxycodone HCl/naloxone HCl) Extended Release Tablets
Indication: Management of (b) (4) pain (b) (4), around-the-clock (b) (4).
Dosages: Oxycodone HCl/Naloxone HCL: 10/5, 20/10, and 40/20 mg tablet strengths
Sponsor: Purdue Pharma L.P.

Materials reviewed: NDA 205-777 Submission

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1 Background

This memorandum is in response to a consult request dated October 17, 2013, from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) concerning NDA 205-777 pertaining to Targiniq (Oxycodone HCl/naloxone HCl) Extended Release Tablets under development by Purdue Pharma L.P. This NDA was submitted on September 16, 2013. The Division requested that CSS review NDA 205-777 from an abuse potential perspective.

Targiniq ER is a combination product containing oxycodone hydrochloride and naloxone hydrochloride in a fixed ratio of 2:1. According to Sponsor, the oxycodone component is intended to provide analgesia while the naloxone component is intended to decrease the potential for abuse of the oxycodone component particularly by intravenous, intranasal, (b) (4) routes of administration.

Targiniq ER is intended for oral administration every 12 hours for the management of (b) (4) pain (b) (4), around-the-clock (b) (4) Maximum recommended daily dose is 80 mg oxycodone HCl and 40 mg naloxone HCl (Targiniq ER 40mg/20mg every 12 hours).

2 Conclusions:

Following a review of all information submitted under NDA 205-777, CSS provides below conclusions regarding Targiniq ER tablets.

1. Overall, the data provided from in vitro physical and chemical manipulation studies and human abuse potential studies indicate that Targiniq ER tablets display resistance to abuse by intravenous and intranasal administration, but to a lesser extent to oral administration, depending upon the abusing population.

2. For the population of non-dependent, non-tolerant recreational opioid users manipulation (crushing or extraction from whole tablets in hot water) of Targiniq ER tablets with the intention of intravenous or intranasal administration will most likely result in little or no drug liking due to the presence of naloxone (study ONU1003) in a 2:1 ratio of oxycodone HCl/naloxone HCl that suppresses the mu-opioid agonist effects of oxycodone. However, such individuals may be expected to experience substantial levels of drug liking as well as possible overdose when Targiniq ER tablets are crushed followed by ingestion or when chewed followed by swallowing (see Study ONU1007). This may be attributed to the very low ($\leq$ 2%) absolute oral bioavailability of naloxone as well as to the extensive compromise of the controlled release mechanism for oxycodone HCl and naloxone HCl upon crushing (including crushing by chewing) of Targiniq ER tablets.

3. For the population that is physically dependent and tolerant to opioids, manipulation of Targiniq ER tablets (crushing or extraction from whole tablets in hot water) following by intravenous or intranasal administration will likely elicit a prominent withdrawal syndrome, depending upon the level of physical dependence. With oral administration of crushed Targiniq ER tablets or with chewing of Targiniq ER tablets followed by swallowing, individuals physically dependent and tolerant to opioids will likely experience limited, if any, drug liking. (See Study ONU1008). This may be attributed to the reduced sensitivity of this population to opioid subjective effects as a result of tolerance and to the emergence of at least some levels (mild) of withdrawal.

4. The results of vitro studies indicate that "opioid-naïve or opioid non-tolerant patients" who are initiated with Targiniq ER tablets, may be at risk of potential overdose should

they administer orally crushed Targiniq ER tablets or chew Targiniq ER tablets. Likewise, patients who are physically dependent to opioids (Targiniq ER or other opioid medications) and orally administer crushed Targiniq ER tablets or chew Targiniq ER tablets will likely experience a withdrawal syndrome, the severity of which will depend upon the level of physical dependence.

5. The principal mechanisms underlying the abuse deterrent properties of Targiniq ER tablets are a) the difficulty involved in separating the naloxone HCl from the oxycodone HCl as evidenced in various in vitro studies and b) the effectiveness of the 2:1 ratio of oxycodone HCl to naloxone HCl in blocking the subjective reinforcing effects of oxycodone and potentially precipitating withdrawal.

6. (b) (4)

7. (b) (4)

(See Discussion, Tables 1, 2, and 3)

8. (b) (4)

(See Discussion, Tables 1, 2, and 3)

9. (b) (4)

[redacted] (See Discussion, Tables 2 and 4)

10. Dissolution studies demonstrated that whole Targiniq ER tablets do not dose dump oxycodone HCl and naloxone HCl in simulated gastric fluid containing 40% ethanol. (See Discussion, Table 5)

11. [redacted]

12. [redacted]

13. Results of simulated smoking studies indicate that Targiniq ER tablets most likely cannot be abused by smoking. [redacted]

14. [redacted]

15. [redacted] (See Table 7)

16. [redacted]

17. [redacted] (b) (4)

18. Human abuse potential study ONU1003, using non-dependent opioid experienced subjects, demonstrated that the intravenous injection of 0.035 mg/kg naloxone HCl followed within 1 minute by intravenous injection of 0.07 mg/kg oxycodone HCl solution (simulated 2:1 ratio of oxycodone HCl to naloxone HCl as found in Targiniq ER tablets) produced maximum levels of Drug Liking and High that were similar to that produced by placebo (0.9% NaCl), but well below that produced by oxycodone HCl 0.07 mg/kg solution. In the absence of significant differences in oxycodone HCl plasma levels obtained for the two active treatments, the differences in subjective effects observed, indicate that the 0.035 mg/kg naloxone HCl was effective in reducing the subjective effects of the 0.07 mg/mg oxycodone HCl. The efficacy of the abuse deterrent effect by intravenous administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intravenous injection of the oxycodone HCl and naloxone HCl combination, as compared to injection of just oxycodone HCl. (See Discussion, Tables 9 and 11)

19. Human abuse potential study ONU1003, using non-dependent, opioid-experienced subjects, demonstrated that insufflation of finely crushed Targiniq ER 40/20 mg resulted in maximum Drug Liking and High that were substantially lower than that produced by insufflation of oxycodone HCl 40 mg powder but similar to that of placebo for Drug Liking and higher than placebo for High. As evidenced by scores on the Take Drug Again VAS, the willingness of subjects to insufflate oxycodone HCl 40 mg powder again was much higher than the willingness to take either crushed Targiniq ER 40/20 mg or placebo. The maximum oxycodone plasma concentration (C_{max}) tended to be higher following crushed Targiniq ER than with oxycodone HCl powder alone, with both having similar short time to C_{max} of about 1 hour. The efficacy of the abuse deterrent effect to intranasal administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intranasal administration of Targiniq ER compared to the positive comparator. Again, these data suggest the effectiveness of the naloxone HCl in the Targiniq ER formulation in mitigating the subjective reinforcing effects of oxycodone HCl. (See Discussion, Tables 9 and 10)

20. Human abuse potential study ONU1007, using non-dependent, opioid-experienced subjects, demonstrated that in comparison to oxycodone 40 mg oral solution (active comparator), chewed Targiniq ER 40/20 mg produced similar maximum levels of Drug Liking, High and Take Drug Again. Ingestion of intact Targiniq ER 40/20 mg produced significantly lower levels of Drug Liking, High, and Take Drug Again that were, however, significantly above placebo. The maximum oxycodone plasma level (C_{max}) tended to be similar between chewed Targiniq ER 40/20 mg and oxycodone 40 mg oral solution with a similar median time of C_{max} of 1.05 hours. With ingestion of intact

Targiniq ER 40/20 mg, the oxycodone plasma level was a little less than half that of chewed Targiniq ER 40/20 mg Treatment with intact or chewed Targiniq resulted in only low maximum plasma levels of naloxone, reflecting the very low oral bioavailability (≤ 2%) of naloxone. The high levels of subjective reinforcing effects with chewed Targiniq ER may be attributed to the low levels of naloxone available to antagonize the effects of oxycodone following oral. The lower but still significant levels of subjective effects following ingestion of intact Targiniq ER is most likely due to the controlled release properties of the intact formulation for oxycodone HCl. (See Discussion, Tables 12 and 13)

21. Sponsor conducted human abuse potential study ONU1004 to evaluate the subjective effects of chewed Targiniq ER 30/15 mg and chewed Targiniq ER 60/30 mg in opioid dependent (methadone maintained) subjects. However, a review conducted by the Office of Biostatistics found that with respect to Drug Liking VAS there were no significant differences between 30 mg or 60 mg oxycodone HCl solution (active comparator) and placebo. As such, the Office of Biostatistics concluded that differences between chewed Targiniq ER (either dose) and oxycodone HCl oral solution were not meaningful. A statistical analysis was completed regarding withdrawal scores using the "Subjective Opioid Withdrawal Scale" (SOWS). Subjects treated with Targiniq ER 60/30 mg had a similar maximum SOWS score compared to placebo but significantly high maximum SOWS score compared to oxycodone HCl 60 mg active solution. Only two subjects had a mean maximum SOWS above 10 with the highest being 14, indicating moderate withdrawal.

22. Human abuse potential study ONU1008 demonstrated that opioid dependent, methadone-maintained subjects may be less susceptible to oral abuse, including chewing, of Targiniq ER tablets. This may be due to the presence of tolerance to subjective effects (less sensitivity) and to experiencing the adverse effects of withdrawal. Intact and chewed Targiniq ER 60/30 mg tablets produce similar low levels of Drug Liking and High that were similar to placebo, but significantly lower than that produced by the active comparator oxycodone 60 mg oral solution. The Take Drug Again VAS demonstrated a limited willingness of subjects to take again oxycodone 60 mg oral solution but a desire not to take again either placebo, intact Targiniq ER or chewed Targiniq ER. Data provided by Sponsor showed that chewed Targiniq ER 60/30 mg and oxycodone 60 mg oral solution produced similar maximum oxycodone plasma levels reached at a median of 1.08 and 2.07 hours, respectively. With intact Targiniq ER 60/30 mg maximum oxycodone plasma level was a little less than half that of chewed Targiniq ER and positive comparator with a median time of 3.05 hours. Chewed and intact Targiniq ER treatments resulted in low levels of naloxone in plasma reflecting the poor bioavailability of naloxone following oral administration. The efficacy of the abuse deterrent effect by oral administration on opioid dependent subjects is further demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following treatment with either intact Targiniq ER tablet or chewed Targiniq ER tablet compared to treatment with the positive comparator. (See Discussion, Tables 14 and 15)

23. In human abuse potential study ONU1008, the use of the "Subjective Opioid Withdrawal Scale" (SOWS) (64 point scale) revealed that for all treatments there were opioid dependent (methadone-maintained) subjects who displayed withdrawal, most often mild withdrawal. Treatment with chewed Targiniq ER produced the maximum SOWS scores that, according to Sponsor, were significantly greater than those observed following treatment with placebo, intact Targiniq ER, or oxycodone HCl 60 mg oral solution. Individual subject data revealed that of 29 total subjects, 20, 22, 23, and 19 subjects displayed "mild withdrawal" (SOWS scores 1-10) following treatment with intact and chewed Targiniq ER, oxycodone HCl 60 mg oral solution, and placebo, respectively. Two and 6 subjects displayed severe withdrawal (SOWS score of > 20) following intact and chewed Targiniq ER, respectively. Three and 2 subjects, following placebo displayed moderate (SOWS score 11-20) and severe withdrawal, respectively.

24. As part of the safety assessment Sponsor provided eight case narrative reports obtained from an international drug safety database (manufacturer's adverse effects reporting database: ARGUS) documenting severe withdrawal with hospitalization in subjects who attempted to manipulate (crush) and abuse (intravenous or snorting) oxycodone/naloxone (2:1 ratio) product (i.e., Targin) currently marketed in other countries. (See Discussion, Integrated Assessment)

3 Recommendations:

1. Sponsor should be required to carefully monitor for the oral abuse and potential concomitant overdose of crushed Targiniq ER tablets particularly among recreational opioid users who may manifest a lack of or low level of physical dependence and opioid tolerance. Due to the very low bioavailability of naloxone and to the compromise of the controlled release mechanism of oxycodone HCl and naloxone HCl upon crushing, crushed (including chewed) Targiniq ER tablets are expected to produce high levels of subjective reinforcing effects, analogous to immediate release oxycodone formulation, following ingestion. This outcome is supported by the results of human abuse potential study ONU1007 in which non-dependent subjects chewed Targiniq ER tablets resulting in high levels of Drug Liking.

2. The label should contain clear warnings of possible precipitated withdrawal occurring in individuals who are opioid dependent and purposely attempt to intravenously or intranasally abuse Targiniq ER tablets after crushing. Withdrawal may also be observed in opioid-dependent subjects who attempt to chew Targiniq ER tablets.

3. The language proposed by the Sponsor in Section 9.2 of the label regarding "In Vitro Testing" is appropriate and should be included in the label. This language affirms the results of in vitro testing, namely that although with crushing the controlled release mechanisms are compromised for both oxycodone HCl and naloxone HCl, it is very difficult to use physical and chemical manipulations to separate the naloxone from the oxycodone.

4. The proposed inclusion of language describing human abuse potential studies ONU1003 and ONU1008 should be granted.

4 Discussion:

4.1 Chemistry

4.1.1 Product information

Targiniq ER tablets were developed as a controlled-release oral combination product formulated as a tablet with a fixed 2:1 ratio of oxycodone hydrochloride to naloxone hydrochloride. Tablet strengths include 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg of oxycodone HCl/naloxone HCl.

The release mechanism of the Targiniq ER tablets [redacted (b) (4)]

Other excipients (function) found within the core include: lactose monohydrate [redacted (b) (4)], povidone [redacted (b) (4)] talc [redacted (b) (4)], and magnesium stearate [redacted (b) (4)]. For all tablet strengths, [redacted (b) (4)]

Total tablet weights for Targiniq ER 10mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg strengths are 127.27 mg, 142.17 mg, and 284.34 mg, respectively.

4.1.2 Products with potential abuse deterrent claims

A series of in vitro physical manipulation and chemical extraction studies, as documented in Analytical Sciences Report AS-ONU-12/12 were conducted to evaluate the potential abuse deterrent properties of Targiniq ER tablets to routes of abuse. The overall goals of these studies were to "comprehensively examine the extractability of oxycodone and naloxone from Targiniq ER tablets and to determine the feasibility of separating or inactivating the naloxone antagonist component through a spectrum of physical and chemical manipulations. Studies were conducted by independent, third party laboratories [redacted (b) (4)] and [redacted (b) (4)]. All three dosage strengths of Targiniq ER tablets were evaluated in these studies. All testing conditions were analyzed using at least 5 replicates.

Sponsor noted that an appropriate comparator to Targiniq ER does not exist. Therefore, the free base and hydrochloride salt forms of the APIs (oxycodone and naloxone) were used as controls "when necessary to understand the performance of a specific method."

Study 1. Physical Manipulation and Generation of Test Articles

According to Sponsor, Targiniq ER tablets are not formulated to resist crushing. Tablets were

(b) (4)

4.2 **Clinical Studies**

4.2.1 Human abuse potential studies

Sponsor submitted the following human abuse potential studies in support of the NDA:

- Study ONU1003 entitled "A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets Administered via the Oral, Intranasal, and Intravenous Routes." Statistical review was completed by the Office of Biostatistics (DARRTS, NDA205-777, February 11, 2014, Author: Ling Chen, Ph.D.)
- Study ONU1004 entitled "A Single-Center, Randomzied, Double-Blind Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) in Opioid Dependent Subjects." Statistical review was completed by the Office of Biostatistics (DARRTS, NDA205-777, February 11, 2014, Author: Ling Chen, Ph.D.)
- Study ONU1007 entitled "A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse-Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets When Chewed or Administered Via the Oral Route" Statistical review was completed by the Office of Biostatistics (DARRTS, NDA205-777, February 11, 2014, Author: Anna Sun, Ph.D.)
- Study ONU1008 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Intact and Chewed Oxycodone/Naloxone (ONU) Tablets in Opioid-Dependent Subjects." Statistical review was completed by the Office of Biostatistics (DARRTS, NDA205777, February 11, 2014, Author: Anna Sun, Ph.D.).

In support of NDA 205-777 Sponsor also submitted study ONU9001 entitled "Relative Attractiveness of Oxycodone/Naloxone (ONU): Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations." This study was completed in July 2010.

Study ONU1003

Overall, this study based on a primary analysis of E_{max} of Drug Liking VAS, indicates that chewed Targiniq ER 40/20 mg has an abuse potential similar to that of oxycodone HCl oral solution 40 mg, whereas the abuse potential of Targiniq ER 40/20 administered intranasally or intravenously is significantly reduced to near placebo-like effects. These results are in keeping with the low oral ($\leq$ 2%) bioavailability and high intranasal and intravenous (100%) bioavailability of naloxone HCl.

Study ONU1003 was a single-center, double-blind, parallel-group, randomized crossover study to evaluate the abuse potential of Targiniq ER in healthy non-dependent recreational drug users with moderate experience with opioids and to evaluate the safety and PK profiles of both oxycodone and naloxone, when administered orally, intranasally, or intravenously. Subjects were divided into 3 parallel groups (cohorts), separated by route of administration. Study consisted of 4 phases including: screening (including naloxone challenge), qualification, treatment, and follow-up. Treatment Phase consisted of 3 visits, each lasting 3 days (2 overnight stays) for Groups 1 and 2 and 2 days (1 overnight stay) for Group 3.

To be eligible for the Treatment Phase subjects had to pass the following criteria during the Qualification Phase:

- Peak scores (E_{max}) in response to oxycodone greater than that of placebo on "at the moment" Drug Liking VAS (difference of at least 15 points, or 30% on this bipolar scale) and Overall Drug Liking VAS (difference of at least 10 points, or 20%, on this bipolar scale.
- Acceptable responses to placebo and oxycodone on Drug Liking VAS, ARCI MBG, and Overall Drug Liking, as judged by the investigator and/or designee.
- Ability to tolerate oxycodone as judged by the investigator.
- General behavior suggestive that subject would successfully complete study.

For groups 1, 2, and 3 the primary endpoint was E_{max} of bipolar Drug Liking VAS. Other measures included unipolar High VAS, ARCI MBG, unipolar Good Effects VAS, unipolar Bad Effects VAS, bipolar Overall Drug Liking VAS and bipolar Take Drug Again VAS. This review will focus on Drug Liking VAS, High VAS, and Take Drug Again VAS.

For the three groups pharmacokinetic parameters of C_{max}, T_{max} and total drug exposure (AUC_{inf}) were determined for oxycodone HCl and naloxone HCl.

Group 1 – Chewing Study

Group 1 consisted of subjects who had experience on at least 3 occasions of chewing, grinding, or crushing opioid medications for the purpose of recreational abuse/misuse in the last 12 months. There were 14 completers who received during the Treatment Phase (6 sequences based on two 3x3 William squares) the following treatments in a randomized, double-blind, double-dummy fashion (1 per treatment visit):

- Targiniq ER 40/20 tablet, chewed + placebo solution

- Oxycodone HCl oral solution 40 mg (mixed in juice to approximately 24 mL) + matching placebo tablet, chewed
- Treatment C: placebo solution (approximately 240 mL of juice alone) + matching placebo tablet, chewed.

Subjects were instructed to chew the Targiniq ER/placebo tablet approximately (b) (4) (b) (4) without swallowing. A mouth check was performed by staff to ensure that tablet had been chewed and broken into small pieces. If large pieces were visible, subject was instructed to chew (b) (4) without swallowing. After tablet consumption, subjects were required to consume 50 to 100 mL of water.

PD assessments were taken at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post-dosing.

PK was assessed pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose

Pharmacokinetic Results:

The oxycodone mean (SD) C_{max} of chewed Targiniq 40/20 mg (87.51 $\pm$ 24.97 ng/mL) occurring with a median (range) T_{max} of 0.550 (0.25-1.05) hours was similar to that seen following treatment with oxycodone 40 mg oral solution (84.87 $\pm$ 32.74 ng/mL at median T_{max} of 0.567 (0.53-3.07) hours). Total exposure to oxycodone expressed as AUC_{inf} was similar to both treatments (552.0 $\pm$ 172.24 h.ng/mL versus 549.7 $\pm$ 170.85 h.ng/mL).

Chewing of Targiniq 40/20 mg tablet caused the release of naloxone as evidenced by mean (SD) plasma naloxone C_{max} of 0.4004 $\pm$ 0.254 ng/mL with a median (range) T_{max} of 0.550 (0.25-1.05) hours. Total naloxone exposure (AUC_{inf}) was 1.548 $\pm$ 0.654 h.ng/mL.

Pharmacodynamic Results

Descriptive statistics for E_{max} of Drug Liking, High, and Take Drug Again VAS for the three treatments are found in Table 8. Inferential statistics were not conducted due to limited population and due to the clear differences in scores between active treatments compared to placebo on the three scales. Chewing of Targiniq ER 40/20 mg tablet and ingestion of oxycodone HCl 40 mg oral solution produced high mean maximum (E_{max}) scores for Drug Liking (92.36 and 94.43, respectively) and High (85.64 and 96.93), respectively, that were well above placebo (54.50 for Drug Liking and 19.64 for High).

Table 8. Descriptive Statitistics for E_{max} of Drug Liking, High, and Take Drug Again for Chewed Targiniq ER 40/20 mg, Oxycodone HCl 40 mg Oral Solution, and Placebo.

VAS		Targiniq ER 40/20 mg Tablet Chewed	Oxycodone HCL 40 mg Oral Solution	Placebo Solution
Bipolar Drug Liking	Mean (SE)	92.36 (4.16)	94.43 (3.09)	54.50 (6.02)
	Median (Range)	100 (51-100)	100 (66-100)	51 (50-83)
Unipolar High	Mean (SE)	85.64 (7.33)	96.93 (2.39)	19.64 (9.07)
	Median (Range)	99.5 (0-100)	100 (67-100)	0 (0-100)
Bipolar Take Drug Again	Mean (SE)	84.71 (5.05)	89.79 (4.60)	32.57 (8.5)
	Median (Range	100 (51-100)	100 (50-100)	50 (0-100)

As evidenced by the scores on the "Take Drug Again" VAS, subjects were more willing to chew Targiniq 40/20 tablet and ingest oxycodone 40 mg solution than to ingest placebo solution. The high E_{max} values for Drug Liking, High, and Take Drug Again following chewing of Targiniq 40/20 mg tablet is most likely due to the poor bioavailability ($\leq$ 2%) of naloxone HCl when administered orally. Although naloxone was detected in plasma following chewing of Targiniq ER tablet, the amount was low and not sufficient to block the subjective reinforcing effects of the oxycodone HCl.

Table 9 provides percentage reduction in E_{max} of Drug Liking with chewed Targiniq ER 40/20 mg tablet compared to ingestion of oxycodone HCl 40 mg oral solution. Only four subjects chewing Targiniq displayed an E_{max} of drug liking less than that of oxycodone 40 mg solution ingested. Out of 14 total subjects chewing Targiniq ER tablets, three subjects (21%) displayed at least a 30% reduction and one 1 subject a 50% reduction in E_{max} of Drug Liking compared to treatment by ingestion of oxycodone HCl 40 mg oral solution.

Table 9. Percentage Reduction in E_{max} of Drug Liking for Targiniq ER (40/20 mg) Chewed (Group 1), Targiniq ER (40/20 mg) Insufflated (Group 2), and Intravenously Injected (Group 3) Simulated Targiniq ER (Oxycodone HCl/Naloxone HCl 0.07/0.035 mg/kg) Compared to Appropriate Control Oxycodone HCl API.

Bipolar VAS of Drug Liking	Group 1 (N=14) Chewed Targiniq 40/20 mg vs. Oxycodone 40 mg Oral Solution		Group 2 (N=23) Insufflated Targiniq 40/20 mg powder vs. Oxycodone 40 mg Powder		Group 3 (N=22) I.V. Oxycodone/Naloxone 0.07/0.035 mg/kg vs Oxycodone HCl 0.07 mg/kg	
Percentage of Reduction (%)	Frequency	Percentage of subjects (%)	Frequency	Percentage of Subjects (%)	Frequency	Percentage of Subjects (%)
>0	4	29	19	83	21	95
≥10	3	21	19	83	21	95
≥20	3	21	19	83	21	95
≥30	3	21	18	78	20	91
≥40	2	14	17	74	20	91
≥50	1	7	17	74	20	91
≥60	1	7	17	74	20	91
≥70	0	0	16	70	19	86
≥80	0	0	14	61	18	82
≥90	0	0	13	57	17	77
≥100	0	0	4	17	2	9

Group 2 – Intranasal Study

Group 2 consisted of subjects who had experienced at least 3 occasions of intranasal opioid use for the purpose of recreational abuse/misuse in the last 12 months. There were 23 completers who received during the Treatment Phase (6 sequences based on two 3x3 William squares) the following treatments in a randomized, double-blind, fashion (1 per treatment visit):

- Targiniq ER 40/20 mg, finely crushed

- Oxycodone HCl API powder 40 mg
- Lactose Powder Placebo

Subjects were instructed to snort the treatments (b) (4) The same nostril was to be used for administration within each period; however, nostril side could be changed from period to period. Subjects were not allowed to blow their nose for 1 hour post-dose.

PD assessments were taken at 0.25, 0.5, 2, 3, 4, 6, and 24 hours

PK assessments were conducted pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

Intranasal irritation was assessed by the ears, nose and throat (ENT) specialist, investigator, or designee (categories of nasal congestion, nasal irritation external, nasal discharge) and by study subjects (categories of burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, nasal congestion). Assessments were made using a 6-point scale (0=Not observed/No problem, 1=Very Mild Problem; 2=Mild/Slight Problem; 3=Moderate Problem; 4=Severe Problem; to 5=Very Severe Problem/"As Bad as Can Be").

Pharmacokinetic Results

Insufflation of crushed Tarqiniq ER 40/20 mg tablet resulted in oxycodone C_{max} (SD) and T_{max} (range) of 90.1 $\pm$ 32.08 ng/mL and 1.075 (0.57-3.07) hours, respectively. Insufflation of oxycodone HCl 40 mg powder resulted in a C_{max} (SD) and T_{max} of 69.78 $\pm$ 19.24 ng/mL and 1.108 (0.28 - 4.07) hours, respectively. Both treatments produced similar total exposure to oxycodone (AUC_{inf}) at around 588 to 590 h.ng/mL.

Following insufflation of crushed Targiniq ER 40/20 mg tablet but not of oxycodone HCl 40 mg powder, naloxone was found in plasma (C_{max} of 20.15 $\pm$ 5.71 ng/mL, T_{max} of 0.300 (0.28 – 0.73) and AUC_{inf} of 29.93 $\pm$ 12.47 h.ng/mL).

Pharmacodynamic Results:

Descriptive statistics for E_{max} of Drug Liking, High, and Take Drug Again for the three treatments are found in Table 10. The Office of Biostatistics did not calculate inferential statistics for Emax of Drug Liking due to the obvious difference between treatments.

As is evident from Table 10, insufflation of oxycodone HCl 40 mg powder produced scores of Drug Liking, High and Take Drug Again that were clearly above those scores produced by insufflation of either Targiniq ER 40/20 mg finely crushed powder or placebo powder. According to Sponsor, insufflation of Tarqiniq ER powder resulted in a mean E_{max} of High (36.2) that was significantly above that of placebo (8.3). Subjects documented a lower willingness to take again either insufflated Targiniq ER 40/20 mg powder (mean E_{max} of 42.61) or placebo (mean E_{max} of 30.74), as opposed to insufflated oxycodone HCl 40 mg powder (mean E_{max} 93.57).

Table 10. Descriptive Statistics for E_{max} of Drug Liking, High, and Take Drug Again for Insufflation of Targiniq ER 40/20 mg Finely Crushed Powder, Oxycodone HCl 40 mg Powder, and Placebo (Lactose Powder). (N = 23)

VAS		Targiniq ER 40/20 Finely Crushed	Oxycodone HCL 40 mg Powder	Placebo (Lactose Powder)
Bipolar Drug Liking	Mean (SE)	59.13 (2.84)	94.83 (2.18)	53.17 (2.14)
	Median (Range)	51 (50-100)	100 (61-100)	51 (50-100)
Unipolar High	Mean (SE)	36.22 (7.44)	92.74 (4.52)	8.30 (4.91)
	Median (Range)	47 (0-100)	100 (0-100)	0 (0-100)
Bipolar Take Drug Again	Mean (SE)	42.61 (6.37)	93.57 (2.31)	30.74 (6.09)
	Median (Range	50 (0-100)	100 (62-100)	50 (0-100)

Table 9 provides percentage reduction in E_{max} of Drug Liking with insufflation of Targiniq 40/20 mg powder compared to insufflation with oxycodone HCl 40 mg powder. Out of 23 total subjects, 4 subjects did not show any percentage reduction in E_{max} of Drug Liking while 18 (78%) and 17 (74%) subjects displayed 30% and 50% reductions in Drug Liking E_{max}, respectively.

Subject rated assessments of intranasal irritation revealed that the three treatments produced little nasal irritation. Sponsor conducted analysis showed that with pairwise comparisons insufflation of Targiniq ER 40/20 mg was associated with a higher median E_{max} score on nasal congestion compared to placebo ($p < 0.05$). All other differences were very small.

Group 3 – Simulated Intravenous Injection

Group 3 consisted of subjects who had experience with opioids using multiple routes ($\geq$2) of administration (e.g. oral, intranasal, intravenous) for the purpose of recreational abuse/misuse. There were 22 completers who received during the Treatment Phase (6 sequences based on two 3x3 William squares) the following intravenous treatments in a randomized, double-blind fashion (1 per treatment visit):

- Simulated Targiniq ER: 0.035 mg/kg naloxone HCl in saline solution via bolus injection, followed within approximately 1 minute by 0.07 mg/kg oxycodone solution (approximately 1 minute infusion)
- Saline alone via IV bolus injection (within approximately 1 minute), followed within approximately 1 minute by 0.07 mg/kg oxycodone HCl solution (approximately 1 minute infusion)
- Placebo: Saline alone via IV bolus injection, followed within approximately 1 minute by saline alone (approximately 1 minute infusion).

PD assessments were conducted at 5 minutes and at 0.25, 0.5, 0.75, 1, 2 and 8 hours post-dosing

PK assessments were conducted pre-infusion and 0.083 (5 minutes), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours after start of infusion.

Pharmacokinetic Results:

Intravenous injection of oxycodone 0.07 mg/kg + naloxone 0.035 mg/kg resulted in oxycodone C_{max} (SD) and T_{max} (range) of 95.56 + 44.11 ng/mL and 0.05 (0.05 - 0.22) hours, respectively. Intravenous injection of oxycodone HCl 0.07 mg/kg resulted in a C_{max} (SD) and T_{max} of 83.08 $\pm$ 37.6 ng/mL and 0.05 (0.05 - 8.03) hours, respectively. Both treatments produced similar total exposure to oxycodone (AUC_{inf}) at around 114.7 to 116.4 h.ng/mL.

Following intravenous injection of oxycodone HCl 0.07 mg/kg + 0.035 mg/kg naloxone HCl but not intravenous injection of oxycodone HCl 0.07 mg/kg, naloxone was found in plasma (C_{max} of 25.27 + 11.69 ng/mL, T_{max} of 0.05 (0.05 – 0.05) and AUC_{inf} of 12.73 $\pm$ 2.55 h.ng/mL).

Pharmacodynamic Results

Descriptive statistics for E_{max} of Drug Liking, High, and Take Drug Again for the three intravenous treatments are found in Table 11. The Office of Biostatistics did not calculate inferential statistics for E_{max} of Drug Liking due to the obvious difference between treatments.

As is evident from Table 11, intravenous injection of oxycodone HCl 0.07 mg/kg produced mean E_{max} of Drug Liking (96.36), High (92.32), and Take Drug Again (82.00) that were clearly above those scores produced by intravenous injection of either oxycodone/naloxone 0.07/0.035 mg/kg (56.55, 19.55 and 36.95, respectively) or placebo saline (48.68, 2.91, and 34.50 respectively). According to Sponsor, injection of oxycodone HCl/naloxone HCl 0.07/0.035 mg/kg was not statistically significantly different from placebo with respect to either Drug Liking or High. Subjects documented a lower willingness to take again either intravenous oxycodone HCl/naloxone HCl 0.07/0.35 mg/kg or placebo, as opposed to intravenous oxycodone

Table 11. Descriptive Statistics of Emax for Drug Liking, High, and Take Drug Again Following I.V. Administration of Oxycodone + Naloxone, Oxycodone, and Placebo in Non-Dependent Subjects (N=22).

VAS		Oxycodone/Naloxone 0.07/0.35 mg/kg	Oxycodone HCL 0.07 mg/kg	Placebo Saline (0.9% NaCl)
Bipolar Drug Liking	Mean (SE)	56.55 (2.85)	96.36 (2.30)	48.68 (2.32)
	Median (Range)	51 (50-100)	100 (50-100)	51 (0-53)
Unipolar High	Mean (SE)	19.55 (7.12)	92.32 (4.97)	2.91 (2.49)
	Median (Range)	0 (-1-100)	100 (0-100)	0 (0-55)
Bipolar Take Drug Again	Mean (SE)	36.95 (6.8)	82.00 (6.05)	34.50 (5.15)
	Median (Range	50 (0-100)	99 (0-100)	50 (0-55)

HCl 0.07 mg/kg. The substantial reduction of Emax of Drug Liking, High, and Take Drug Again associated with the intravenous injection of oxycodone/naloxone 0.07/0.035 mg/kg attests to the effectiveness of the naloxone to block these subjective effects produced by oxycodone.

Table 9 provides percentage reduction in Emax of Drug Liking with intravenous injection of oxycodone HCl/naloxone HCl 0.07/0.35 mg/kg compared to intravenous injection with oxycodone HCl 0.07 mg/kg solution. Out of 22 total subjects, 21 subjects display some percentage reduction in Emax of Drug Liking. Twenty subjects (91%) displayed at least a 60% reduction in Drug Liking Emax when injecting oxycodone HCl/naloxone HCl 0.07/0.35 mg/kg solution compared to injecting oxycodone HCl 0.07 mg/kg solution.

Study ONU1004

Study ONU1004 was a single-center, randomized, double-blind, block-order, crossover study to evaluate the pharmacodynamic effects (subjective, physiologic, and withdrawal), pharmacokinetics and oral safety of oral Targiniq ER (chewed) compared to oxycodone HCl API in methadone opioid –dependent subjects (20 to 40 mg/day for at least 14 days prior to screening visit). Study consisted of a Screening Phase, Treatment Phase, and Follow-up. There was no drug discrimination phase.

Treatment Phase consisted of 2 sessions, each lasting 4 days with 3 overnight visits. Subjects under fasted conditions received study drugs according to a randomized block-order design, with each block consisting of two 3 x 3 Williams squares. In the first block, 18 subjects received the following study drugs, each separated by an interval of approximately 24 hours:

- Targiniq ER Tablet 30 mg/15 mg Chewed
- 30 mg Oxycodone HCL in solution
- Placebo

Following an interval of 3 days, 16 subjects were randomized to session 2 and received the following treatments:

- Targiniq ER Chewed 60/30 mg
- 60 mg Oxycodone HCl in solution
- Placebo

Subjects were instructed to chew the Targiniq ER or placebo tablets approximately 10 times with their molars without swallowing; both tablets of the study drug were chewed at the same time. A mouth check (without a tongue depressor) was performed by study staff to ensure that the tablets had been chewed and broken into small pieces. If large pieces of the tablets were visible, subjects were instructed to chew approximately 4 to 5 more times without swallowing, and another mouth check (without a tongue depressor) was performed by staff to ensure the tablet was broken into small pieces. Chewed material was ingested with 240 mL of solution. Other treatments included ingestion of 240 mL of Oxy API or placebo solutions. Placebo solution consisted of juice.
Pharmacodynamic assessments were performed up to 4 hours post-dosing. Pharmacokinetic assessments were conducted up to 8 hours post-dosing.

Pharmacodynamic assessments included bipolar VAS scales for Drug Liking, Take Drug Again VAS, and Overall Drug Liking as well as unipolar VAS scales for Good Effects, High, Bad Effects, Feeling Sick, Any Effects, and Drowsiness/Alertness." There was no clear designation of primary measures verses secondary measures.

Two opioid withdrawal scales were used, namely the "Subjective Opioid Withdrawal Scale" designated SOWS and the Objective Opioid Withdrawal Scale, designated OOWS.

SOWS contain 16 symptoms rated in intensity by patients on a 5-point scale as follows: 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. Total score is a sum of the item ratings, and ranges from 0 to 64. Mild withdrawal is considered to be a score of 1-10. Moderate withdrawal is considered to be a score of 11 to 20. Severe withdrawal is considered to be 21 – 30.

The OOWS contains 13 physically observable signs, rated as "present" or 'absent", based on a timed period of patient observation by a rater. Range of total scores is 0 to 13.

Pharmacokinetic Results

The pharmacokinetic population consisted of 18 subjects in session 1 and 16 subjects in session 2.

Mean C_{max} and AUC_{last} were slightly higher for Oxy API compared with Targiniq ER for both Treatment Sessions.

For Targiniq ER 30/15 mg and Oxycodone HCl API 30 mg treatments mean oxycodone (SD) C_{max} were 65.9 $\pm$ 16.37 ng/mL and 76.1 $\pm$ 11.77 ng/mL, respectively, while the mean (SD) oxycodone AUC_{last} were 301.2 $\pm$ 74.58) and 330.9 $\pm$ 66.90 ng.h/mL, respectively.

For Targiniq ER 60/30 mg and Oxy API 60 mg treatments mean oxycodone (SD) C_{max} were 125.4 $\pm$ 45.21 ng/mL and 148.1 $\pm$ 31.80 ng/mL, respectively, while the mean (SD) oxycodone AUC_{last} were 580.1 $\pm$ 218.32 and 638.8 $\pm$ 170.41 ng.h/mL, respectively. Median T_{max} for oxycodone was approximately twice as long following Targiniq ER 60/30 mg treatment (2.1 hours) as with oxycodone HCl API 60 mg (1.10 hours).

Treatment with Targiniq ER 30/15 mg (session 1) and Targiniq ER 60/30 mg (session 2) resulted in exposure to naloxone as evidenced by mean (SD) C_{max} of naloxone (0.26 $\pm$ 0.110 ng/mL and 0.37 $\pm$ 0.166 ng/mL, respectively) and by mean AUC_{last} (0.74 $\pm$ 0.253 and 1.12 $\pm$ 0.436 ng.h/mL, respectively). Median T_{max} for naloxone of 1.1 hours was reached following treatment with either Targiniq ER 30/15 mg or Targiniq ER 60/30 mg.

Pharmacodynamic Results:

According to the Sponsor and the Office of Biostatistics there were no significant differences between 30 mg oxycodone API and placebo with respect of Drug Liking or other positive subjective abuse potential measures in Treatment session 1. There were also no significant differences between 60 mg oxycodone API and placebo on Drug Liking, Overall Drug Liking, and Take Drug Again VAS. Review by the Office of Biostatistics demonstrated that 78% (14/18) and 56% (7/16) of subjects had E_{max} of Drug Liking VAS of less than 60 for 30 mg oxycodone API and 60 mg oxycodone API, respectively. In light of these results, the Office of Biostatistics concluded that comparisons between Targiniq ER and Oxycodone HCl API on these measures are not meaningful.

Results – Withdrawal Measured by OOWS and SOWS

The Office of Biostatistics conducted statistical analyses for E_{max} of OOWS and E_{max} of SOWS for treatment sessions 1 and 2. OOWS consists of a scale ranging from 0 to 13 and the SOWS ranges from 0 to 64

No statistically significant differences were observed between treatments in Session 1 with regard to either E_{max} of OOWS or E_{max} of SOWS. The median difference in the E_{max} between chewed Targiniq ER 30/15 mg and placebo was zero. The mean (SE) E_{max} for OOWS for Targiniq ER 30/15 mg was 1.06 (0.45) with only 3 subjects getting scores above 2.5. The mean (SE) E_{max} for SOWS for Targiniq ER 30/15 mg was 6.44 indicating at most mild withdrawal in some subjects. Two subjects had SOWS scores above 20, indicating severe withdrawal.

Under session 2 there were no significant differences between treatments for E_{max} of OOWS. With regard to E_{max} of SOWS there was a significant increase produced by Targiniq ER 60/30 mg (mean (SE) of 5.63 (1.15) compared to oxycodone HCl API 60 mg (mean (SE) of 0.13 (1.03)), but no difference with respect to placebo (mean (SE) of 1.75 (0.66)). Only two subjects had E_{max} of COWS above 10 with the highest being 14, thereby indicating moderate withdrawal.

Study ONU1007

Study ONU1007 was a single-center, double-blind, randomized, crossover study having the objective to evaluate the abuse potential, pharmacokinetics, and safety of Targiniq ER tablets and intact Targiniq ER tablets compared to oxycodone oral solution and placebo (PBO) in health, adult, non-dependent recreational opioid users with a history of oral chewing abuse/misuse. Study consisted of 4 phases including Screening Phase, Qualification Phase, Treatment Phase, and follow-up. Subjects were subjected to naloxone challenge test to ensure they were not physically dependent to opioids.

During the double blind Qualification Phase subjects were required to distinguish between oxycodone 40 mg oral solution (mixed in juice to about 240 mL) and matching control, comprising a solution of about 240 mL of juice alone. Subjects were required to meet the following criteria:

- Peak scores (E_{max}) in response to oxycodone greater than that of PBO on 'at this moment' Drug Liking visual analog scale (VAS; difference of at least 15 points, or 30%, on this bipolar scale) and Overall Drug Liking VAS (difference of at least 10 points, or 20%, on this bipolar scale).
- Acceptable responses to PBO and oxycodone on Drug Liking VAS, High VAS, Overall Drug Liking VAS, and Take Drug Again VAS, as judged by the investigator and/or designee.
- The ability to tolerate oxycodone, as judged by the investigator or designated subinvestigator based on available safety data.
- General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

Thirty-seven subjects were randomized to the Treatment Phase and received at least 1 dose of the study drug, thereby comprising the Safety Population. One (2.7%) subject discontinued after

Treatment Period 1 for administrative reasons. In total, 36 subjects completed all 4 Treatment Periods including all protocol-specified procedures and assessments. All 36 subjects were included in the PK and PD populations.

Treatment Phase consisted of 4 visits (periods), each lasting 3 days. Subjects received each of the following treatments in a randomized, double-blinded, triple-dummy fashion (one per Treatment visit):

- Targiniq ER 40/20 mg tablet intact
- Targiniq ER 40/20 mg tablet chewed
- Oxycodone HCl 40 mg oral solution
- Placebo

Targiniq ER PBO tablets contained similar excipients to that of Targiniq ER 40/20 mg tablets and were colored and debossed in the same manner but did not contain oxycodone.

Subjects were instructed to chew the Targiniq ER 40/20 mg tablet and PBO tablet approximately 8 to 10 times with their molars without swallowing. A mouth check was performed by staff to ensure the tablet had been chewed and broken into small pieces. If large pieces of the tablet were visible, the subject was instructed to chew approximately 4 to 5 more times without swallowing. Another mouth check was performed to ensure the tablet was broken into small pieces. Subjects were instructed to swallow the tablet pieces with 50 mL of water. Intact tablets were ingested with 240 mL of water the chewed tablets were swallowed.

Pharmacodynamic measures included the bipolar VAS scales for Drug Liking, Overall Drug Liking, Take Drug Again, and Alertness/Drowsiness as well as the unipolar VAS scales of High, Good Effects, Bad Effects, Any Effects, and Feeling Sick. The Addiction Research Center Inventory and Subjective Drug Value procedure was also conducted. The Objective Opioid Withdrawal Scale (OOWS) was used to evaluate opioid withdrawal.

Pharmacodynamic assessments were conducted at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Overall drug liking and take drug again VAS were conducted at 12 hours and 24 hours.

Blood samples for PK analysis of oxycodone and naloxone were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dosing. PK parameters determine were maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the concentration-time curve extrapolated to infinity (AUC_{inf}).

Pharmacokinetic Results

Pharmacokinetic data was obtained from 36 subjects.

Treatment with chewed Targiniq ER 40/20 mg and oxycodone HCl 40 mg oral solution resulted in mean (SD) oxycodone plasma C_{max} of 89.1 $\pm$ 25.0 ng/mL and 81.4 $\pm$ 22.5 ng/mL, respectively, with a similar median (range) of T_{max} (1.05 (0.55-6.02) and 1.05 (0.55-3.05) hours. By contrast, treatment with intact Targiniq ER 40/20 mg resulted in a mean oxycodone C_{max} (39.7 $\pm$ 9.33 ng/mL) that was a little under half that of the other two active treatments. T_{max} for intact

Targiniq ER was about 3 times longer than that of either chewed Targiniq ER or oxycodone HCl oral solution.

The mean (SD) of the AUC_{inf} for intact Targiniq ER, chewed Targiniq ER, and oxycodone HCl oral solution were 518 ± 140, 555 ± 173, and 529 ± 134 h.ng/mL, respectively. These numbers showed that the three treatments provided essentially similar total oxycodone exposure. Treatment with either intact or chewed Targiniq ER 40/20 mg resulted in low exposure to naloxone as evidenced by mean (SD) Cmax values (0.201 ± 0.23 ng/mL and 0.539 ± 0.25 ng/mL, respectively) and mean (SD) AUCinf values (2.03 ± 1.38 h.ng/mL and 2.52 ± 1.59 h.ng/mL, respectively). The time to maximum naloxone concentration (T_{max}) was prolonged for intact Targiniq ER (median (range) of 1.57 (0.25-12.1) hours) compared to chewed Targiniq ER (median (range) of 0.567 (0.25-12.0) hours).

Pharmacodynamic Results – Drug Liking

Descriptive statistics for E_{max} of Drug Liking, High, and Take Drug Again following the various treatments are found in Table 12. Inferential statistics utilized a mixed-effect model with treatment as a fixed effect and subjected nested within sequence as a random effect.

As can be seen from Table 12 chewing Targiniq ER 40/20 produced a mean E_{max} of drug liking (86.3) that was not significantly different ($p = 0.4383$) from that of Oxycodone 40 mg Oral Solution (E_{max} of 88.5). Both of these treatments did produce drug liking that was significantly higher ($p < 0.0001$) than that produced by either intact Targiniq ER 40/20 ($E_{max} = 72.5$) or to placebo ($E_{max} = 50$). In addition, the intact Targiniq ER 40/20 produced E_{max} of Drug Liking that was greater ($p < 0.0001$) than that produced by placebo.

A similar treatment effect pattern to that seen with drug liking was observed for drug high. Chewed Targiniq ER 40/20 produced a similar ($p = 0.5197$) mean Emax of high (87.2) to that of oxycodone HCl 40 mg oral solution but a significantly larger ($p < 0.0001$) mean high Emax compared to either intact Targiniq ER 40/20 (Emax = 59.2) or placebo (Emax = 13.4). Oral administration of intact intact Targiniq ER 40/20 did produce a high significantly ($p < 0.0001$) above that of placebo.

Table 12. Descriptive Statistics for E_{max} of Drug Liking, High, and Take Drug Again (12 Hours) for Oral Administration of Intact Targiniq ER 40/20 mg ER, Oxycodone 60 mg Oral Solution, and Placebo and for Chewed Followed by Oral Administration of Targiniq ER 40/20 in Non-Dependent, Opioid Experienced Subjects. (N=36) (* Data from Sponsor)

VAS		Targiniq ER 40/20 mg Intact	Targiniq ER 40/20 mg Chewed	Oxycodone 40 mg Oral Solution	Placebo Chewed and Intact Tablet, oral solution
Bipolar Drug Liking	Mean (SE)	72.5 (3.2)	86.3 (2.7)	88.5 (2.8)	50 (0.1)
	Median (Range)	73.5 (50-100)	96.0 (51-100)	100.0 (50-100)	51 (50-52)
Unipolar High	Mean (SE)	59.2 (6.2)	87.2 (3.0)	90.5 (3.1)	13.4 (4.1)
	Median (Range)	66.5 (15-100)	100,0 (22-100)	100.0 (15-100)	0.5 (0.0-91)
Bipolar Take Drug* Again 12 hours	Mean (SE)	65.4 (4.3)	78.9 (5.3)	82.6 (4.1)	39.7 (3.6)
	Median (Range	60.5 (0-100)	94.5 (0-100)	100.0 (0-100)	50.0 (0-67)

Statistical analysis conducted by Sponsor showed a similar (p = 0.615) willingness of the study subjects to take again either chewed Targiniq ER 40/20 mg or oxycodone HCl 40 mg oral solution (mean E_{max} scores of 86.3 and 88.5, respectively). They were also more willing (p = 0.004) to chew Targiniq ER 40/20 mg than take intact Tarqiniq ER 40/20 mg (mean score of 65.4). With regard to Take Drug Again VAS, all active treatments were preferred (p < 0.001) over placebo (mean E_{max} of 39.7).

Table 13 provides the percentage reduction in E_{max} of Drug Liking for intact and chewed Targiniq 40/20 mg compared to oxycodone 40 mg oral solution.

Table 13. Percentage Reduction in E_{max} of Drug Liking for Intact and Chewed Targiniq ER 40/20 Tablet Compared to Oxycodone 40 mg Oral Solution. (N = 36)

Bipolar VAS E_{max} of Drug Liking	Targiniq 40/20 mg Chewed Tablet vs Oxycodone 40 mg Oral Solution		Intact Targiniq 40/20 mg Tablet vs. Oxycodone 40 mg Oral Solution	
Percentage of Reduction (%)	Frequency	Percentage of subjects (%)	Frequency	Percentage of Subjects (%)
>0	12	33.33	24	66.67
≥10	12	33.33	23	63.89
≥20	10	27.78	22	61.11
≥30	8	22.22	21	58.33
≥40	7	19.44	20	55.56
≥50	6	16.67	17	47.22
≥60	2	5.56	15	41.67
≥70	1	2.78	12	33.33
≥80	1	2.78	11	30.59
≥90	1	2.78	8	22.22
≥100	0	0	2	5.56

Of 36 total subjects, only 12 showed a lower Emax of Drug Liking with chewed Targiniq ER 40/20 mg compared to ingestion of oxycodone HCl 40 mg oral solution. Of the 24 subjects remaining subjects, 16 displayed an Emax of Drug Liking of 100 while having a placebo response in the range of 50-51. This is in contrast to 20 subjects who had E_{max} of Drug Liking of 100 following ingestion of oxycodone HCl 40 mg oral solution while having a placebo response of 50 or 51. Of a total 36 subjects 8 (22.22%) and 6 (16.67%) had 30% and 50% reductions, respectively, of Drug Liking E_{max} following chewed Targiniq ER 40/20 mg compared to oxycodone HCl 40 mg oral solution.

Of 36 total subjects treated with intact Targiniq ER 40/20 mg tablet, 24 (66.67) showed at least some reduction in E_{max} of Drug Liking compared to that for treatment with oxycodone HCl 40 mg oral solution. Of the 12 subjects that did not show any reduction, 8 subjects had an E_{max} of Drug Liking of 100 while having a placebo response of 50-51. Out of 36 subjects, 21 (58.11%) and 17 (47.22%) had at least 30% and 50% reductions in E_{max} of Drug Liking, respectively, when ingesting intact Targiniq ER 40/20 mg compared to ingestion of oxycodone HCl 40 mg oral solution.

Study ONU 1008

Study ONU1008 is a single-center, double-blind, triple-dummy, randomized, 4-way crossover study to evaluate the pharmacodynamics, pharmacokinetics and safety of oral Targiniq ER 60/30 mg (chewed and intact) compared to Oxy API 60 mg and placebo (PBO) in methadone-maintained (between 20 and 50 mg/day), opioid dependent subjects. Study includes a Screening Phase, Qualification Phase, Treatment Phase, and follow-up.

Under the double-blind Qualification Phase subjects received single oral doses of either Oxy API 60 mg oral solution (240 mL) or placebo (PBO) oral solution (240 mL of juice). A subject was eligible for the treatment phase if the following eligibility criteria were met in the qualification phase:

- Acceptable response to placebo on High VAS (i.e., score <10).
- The ability to tolerate oxycodone, as judged by the investigator or designated sub-investigator based on available safety data.
- General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

Twenty-nine subjects completed all 4 treatment periods and were included in the pharmacokinetic and pharmacodynamic populations.

The Treatment Phase consisted of 1 inpatient session, lasting 9 days with 8 overnight stays. Subjects received each of the listed below, one per treatment period, in a randomized, double-blind, triple-dummy fashion:

- Targiniq ER 60/30 mg intact
- Targiniq ER 60/30 mg chewed
- Oxycodone API, 60 mg oral solution
- Placebo (PBO)

The Targiniq ER doses, Oxy API solutions (mixed in juice to approximately 240 mL), and placebos (matching oral solution and corresponding Targiniq ER placebo tablets) were administered using a triple dummy procedure, with tablets (chewed and intact) and solution treatments at each administration. The Targiniq ER 60/30 mg dose was administered as a 40/20 mg tablet and a 20/10 mg tablet. The Targiniq ER placebo tablets were administered as different colored tablets: 1 to color-match the Targiniq ER 40/20 mg tablet (yellow) and 1 to color-match the Targiniq ER 20/10 mg tablet (red). The Oxy API (60 mg) oral solution was prepared by adding the powder to approximately 240 mL of juice and matching PBO solution consisted of approximately 240 mL juice.

Pharmacodynamic assessments, safety monitoring, and pharmacokinetic sampling were performed until at least 12 hours after each study drug administration in the treatment phase. Subjects received their daily methadone dose after completion of the 4-hour post-dose procedures on days 1, 3, 5, and 7. On days 2, 4, and 6, subjects received their daily methadone dose approximately 20 hours prior to receiving the next dose of study drug.

Subjects were instructed to chew the Targiniq ER/placebo tablets approximately 8 to 10 times with their molars without swallowing. A mouth check (without tongue depressor) was performed by staff to ensure the tablet had been chewed and broken into small pieces. If large pieces of the tablet were visible, the subject was instructed to chew approximately 4 to 5 more times without swallowing. Another mouth check (without tongue depressor) was performed to ensure the tablet was broken into small pieces. Subjects were instructed to swallow the tablet pieces with 50 mL of water. After consumption of the chewed tablet, subjects were administered the intact tablet. Depending on the treatment, 240 mL of the Oxy API or placebo oral solution was given to subjects to ingest the tablet.

Primary measure was E_{max} of unipolar High VAS.

Secondary measures include bipolar Drug Liking VAS (E_{max}, E_{min}, TA_AUE), bipolar Overall Drug Liking VAS (end of session score), bipolar Take Drug Again VAS (end-of-session score), and other VAS scales. This review will focus on the High VAS and Drug Liking VAS.

Two opioid withdrawal scales were used, namely the "Subjective Opioid Withdrawal Scale" designated SOWS and the Objective Opioid Withdrawal Scale, designated OOWS. Both scales were conducted pre-dose and at 1, 2, 3, 4, 8, and 12 hours post-dose.

SOWS contains 16 symptoms rated in intensity by patients on a 5-point scale as follows: 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. Total score is a sum of the item ratings, and ranges from 0 to 64. Mild withdrawal is considered to be a score of 1-10. Moderate withdrawal is considered to be a score of 11 to 20. Severe withdrawal is considered to be 21 – 30.

The OOWS contains 13 physically observable signs, rated as "present" or 'absent", based on a timed period of patient observation by a rater. Range of total scores is 0 to 13.

PK endpoints for oxycodone and naloxone are maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and area under the plasma concentration vs time curve from time zero to last quantifiable concentration (AUC_{last}).

Pharmacokinetic Results:

PK parameters for oxycodone and naloxone were derived from 29 subjects receiving Targiniq 60/30 mg intact and from 28 subjects receiving chewed Targiniq ER 60/30 mg.

According to Sponsor treatment of opioid-dependent subjects with either chewed Targiniq ER 60/30 mg or oxycodone 60 mg oral solution resulted in similar mean oxycodone C_{max} (131 $\pm$ 19.3 ng/mL and 143 $\pm$ 27.0 ng/mL, respectively) and total mean (SD) oxycodone exposures as expressed in AUC_{last} (841 $\pm$ 215 h.ng/mL and 822 $\pm$ 193 h.ng/mL, respectively. Median (range) T_{max} for chewed Targiniq (2.07 (1.07-3.17 hours) was about twice that of oxycodone oral solution (1.08 (1.03-3.07 hours). Compared to these treatments, ingestion of intact Targiniq ER 60/30 mg tablet produced a lower mean (SD) oxycodone C_{max} (72.0 $\pm$ 14.7 ng/mL), with a longer

median (range) T_{max} (3.05 (2.05-8.12) hours) and a lower total mean oxycodone exposure (AUC_{last} of 758 $\pm$ 197 h.ng/mL).

Overall, plasma concentrations of naloxone were low following treatment with intact or chewed Targiniq ER 60/30 mg. Following chewed Targiniq ER naloxone mean (SD) C_{max} (0.352 $\pm$ 0.173 ng/mL) was reached (T_{max}) with a median (range) of 1.08 (1.02-3.07) hours with total mean naloxone exposure of 1.80 $\pm$ 0.605 h.ng/mL. Treatment with intact Targiniq ER 60/30 mg resulted in a lower C_{max} of 0.131 $\pm$ 0.05 ng/mL achieved at (T_{max}) of 2.08 (1.05-12.2 hours. Total mean naloxone exposure following intact Targiniq was 1.56 $\pm$ 0.683 h.ng/mL.

Pharmacodynamic Results

Descriptive statistics for E_{max} of Drug Liking, High, and Take Drug Again (12 hours) using 29 opioid dependent subjects are provided in Table 14. Statistical analysis completed by the Office of Biostatistics utilized a mixed-effect statistical model in which treatment, period, and sequence were fixed effects and subjects nested within sequences were treated as random effect.

Treatment of opioid dependent subjects with intact and crushed Targiniq ER 60/30 mg tablets produced statistically similar ($p = 0.9841$) mean E_{max} of Drug Liking (54.7 and 54.6) that were similar (p = approximately 0.94) to placebo (53.89) but significantly less ($p < 0.0001$) than the mean E_{max} of Drug Liking for oxycodone 60 mg oral solution (77.47). Mean (range) for TE_{max} for oxycodone 60 mg oral solution was 1.000 (0.48-3.00) hours.

As seen in Table 14, the means for E_{max} of High for intact and crushed Targiniq ER 60/30 and for oxycodone 60 mg oral solution were 20.28, 27.57, and 77.80. There were no statistical differences in E_{max} of High between intact and crushed Targiniq ($p = 0.2795$) or between intact or chewed Targiniq versus placebo ($p = 0.8211$ and $p = 0.3906$, respectively). Oxycodone 60 mg oral solution did produce an E_{max} of High that was statistically higher ($p < 0.0001$) than placebo (mean E_{max} of 21.8) or Targiniq ER intact or crushed. The median (range) for TE_{max} were 0.983 (0.48 - 4.00) hours for intact Targiniq ER, 0.500 (0.48 - 8.00) hours for chewed Targiniq ER, and 1.00 (0.50 - 4.00) hours for oxycodone oral solution.

Table 14. Descriptive Statistics for Emax of Drug Liking, High, and Take Drug Again (12 Hours) for Oral Administration of intact Targiniq ER 60/30 ER, Oxycodone 60 mg Solution, and Placebo and for Chewed Followed by Oral Administration of Targiniq ER 60/30 in Methadone Maintained, Opioid Dependent Subjects. (N=29)

VAS		Targiniq ER 60/30 mg Intact	Targiniq ER 60/30 Chewed	Oxycodone 60 mg Oral Solution	Placebo Chewed and Intact Tablet, Oral Solution
Bipolar Drug Liking	Mean (SE)	54.7 (2.0)	54.6 (3.2)	77.9 (3.7)	54.4 (2.1)
	Median (Range)	51.0 (50-99)	51.0 (0-100)	78.0 (50-100)	51.0 (50-100)
Unipolar High	Mean (SE)	20.6 (5.1)	27.7 (6.5)	77.9 (5.0)	21.9 (5.1)
	Median (Range)	1.0 (0-73)	1.0 (0-100)	86.0 (0-100)	1.0 (0-82)
Bipolar Take Drug Again 12 hours	Mean (SE)	38.5 (5.7)	32.6 (5.9)	61.4 (5.9)	41.5 (5.0)
	Median (Range	50 (0-100)	50 (0-100)	50 (0-100)	50 (0-100)

Based on E_{max} of Take Drug Again documented at 12 hours post-dosing, subjects showed a limited willingness to take again oxycodone 60 mg oral solution (E_{max} of 61.4) but demonstrated a desire not to take again either placebo, intact Targiniq ER, or chewed Targiniq ER (means of E_{max} of 41.5, 38.5, or 32.6, respectively).

Table 15. Percentage Reduction of Drug Liking in Opioid Dependent Subjects Receiving Intact or Crushed Targiniq 60/30 mg Tablets Compared to When Treated With Oxycodone 60 mg Oral Solution. (N=29)

Bipolar VAS Emax of Drug Liking	Targiniq 60/30 mg Chewed Tablet vs Oxycodone 60 mg Oral Solution		Intact Targiniq 60/30 mg Tablet vs. Oxycodone 60 mg Oral Solution	
Percentage of Reduction (%)	Frequency	Percentage of subjects (%)	Frequency	Percentage of Subjects (%)
>0	22	75.86	24	82.76
≥10	22	75.86	24	82.76
≥20	21	72.41	24	82.76
≥30	20	68.97	23	79.31
≥40	19	65.52	23	79.31
≥50	19	65.52	23	79.31
≥60	19	65.52	21	72.41
≥70	18	62.07	19	65.52
≥80	15	51.72	16	55.17
≥90	14	48.28	16	55.17
≥100	7	24.14	10	34.48

In the report for study ONU1008 Sponsor did not provide any data regarding percentage reductions in Emax for any subjective effects, including for "Drug Liking" and "High". However the Sponsor, using data from study ONU1008, did insert into Section 9.2 of the label a graph (designed "Figure 3") of percentage reduction of E_{max} for Drug Liking observed with intact and chewed Targiniq 60/30 tablets compared to ingestion of oxycodone 60 mg oral solution. As a result, the Office of Biostatistics conducted percentage reduction analysis of E_{max} of Drug Liking using data from study ONU1008. The resulting analysis is showed in Table 15.

Out of 29 total subjects receiving chewed Targiniq ER 60/30 mg, 22 subjects (75.86%) demonstrated some decrease in E_{max} of Drug Liking, while 20 (68.97%) subjects and 19 (65.52) subjects had 30% and 50% reductions, respectively, in drug liking when treated with chewed Targiniq ER compared to oxycodone HCl oral solution. Only one of the subjects who showed no reduction in drug liking had an E_{max} of drug liking of 100. This same subject also had an Emax of Drug Liking of 100 for oxycodone oral solution at 51 for placebo.

In a comparison of the percentage reduction in E_{max} of Drug Liking following treatment with intact Targiniq ER 60/30 mg compared to oxycodone 60 mg oral treatment, out of 29 total subjects, 24 (82.76%) subjects demonstrated at least some reduction in E_{max} of Drug Liking, while 23 (79.31%) subjects demonstrated at least a 30% and 50% reduction in E_{max} of Drug Liking.

Pharmacodynamic Results – Withdrawal Determined by SOWS and OOWS

Sponsor reported data using the 64-point SOWS scales indicates that most subjects experienced some withdrawal during the Treatment Phase. This withdrawal tended to be highest at 1 hour post-dosing. Chewed Targiniq ER 60/30 mg and placebo produced the highest mean (SD) Emax for SOWS of 9.3 $\pm$ 13.5 and 6.8 $\pm$ 7.97, respectively. Lower levels of withdrawal were associated with oxycodone 60 mg oral solution (E_{max} of 2.7 $\pm$ 2.39) and intact Targiniq 60/30 mg (E_{max} of 4.4 $\pm$ 8.66). Statistical analysis conducted by Sponsor showed that the SOWS Emax for chewed Targiniq ER was significantly higher than that for either intact Targiniq ER 60/30 or for oxycodone HCl 60 mg oral solution.

Examination of individual subject data for SOWS shows that

- For treatment with intact Targiniq ER 60/30 mg 20 subjects displayed mild withdrawal (SOWS scores 1-10) and 2 subjects displayed severe withdrawal (SOWS > 20)
- For treatment with chewed Targiniq ER 60/30 mg, 22 subjects displayed mild withdrawal (SOWS scores 1-10) and 6 subjects displayed severe withdrawal (SOWS > 20).
- For treatment with oxycodone HCl 60 mg oral solution, 23 subjects display mild withdrawal (SOWS scores 1-10)
- For treatment with placebo, 19 subjects displayed mild withdrawal (SOWS 1-10), 3 subjects displayed moderate withdrawal (SOWS 11-20) and 2 subjects displayed severe withdrawal (SOWS > 20)

According to Sponsor, using the 14-point OOWS there were no significant overall treatment effects for OOWS Emax. Mean (SD) Emax values were 1.1 $\pm$ 0.46 for placebo, 1.2 $\pm$ 0.86 for intact Targiniq 60/30 mg, 1.3 $\pm$ 1.04 for chewed Targiniq 60/30 chewed, and 0.9 $\pm$ 0.50 for oxycodone 60 mg oral solution. Largest OOWS scores, reflecting larger withdrawal, was seen at 1 hour post-dosing.

Examination of individual subject data for OOWS shows that

- For treatment with intact Targiniq ER 60/30 mg, 2 subjects each had OOWS E_{max} of 2 and 4 while remainder had OOWS E_{max} of 1.
- For treatment with chewed Targiniq ER 60/30 mg, one subject each had OOWS E_{max} of 3, 4 and 5 while 3 subjects had OOWS scores of 2 and the remainder 1 or 0.
- For treatment with oxycodone HCl 60 mg oral solution, 2 subjects had OOWS E_{max} of 2 while the remainder had E_{max} of 1.
- For treatment with placebo, 1 subject each had OOWS E_{max} of 0, 2, and 3 while remainder of subjects had OOWS E_{max} of 1.

Study ONU9001

Study ONU9001 was conducted with the objective of assessing the attractiveness and tampering on Targiniq ER compared to other oxycodone formulations. Thirty subjects were recruited from a site in Canada. No information was provided on how they were recruited. All subjects were current recreational opioid users.

To be included in the study all subjects

- Had to be current recreational opioid users.
- Had to provide at least 2 examples of pharmaceutical opioid tampering that they had done in the last 24 months (e.g., crushing, snorting, chewing, extraction from multi-ingredient products, etc.) and
- Were required to have a preference for one of 3 routes (oral, i.v. or intranasal) of abusing opioids.

The majority of subjects accepted for study (≥ 50.0%) reported prior experience with original OxyContin, Percocet, Tylenol3s/4s or other codeine products, Dilaudid, morphine products (other than MS Contin®, Kadian®,, MS IR or other immediate-release morphine products), and Percodan®. Opioids also commonly used (25.0% ≥ but < 50.0% subjects) were MS Contin, heroin, and Demerol. Fewer subjects (< 25%) reported prior experience with Oxy IR or other immediate-release oxycodone products, methadone, fentanyl, hydrocodone, Kadian, immediate-release morphine, or 'other' opioid products, and no subject reported use of Opana (oxymorphone). The opioids most commonly tampered with (≥ 50.0% of subjects) were OxyContin®, Percocet, Tylenol 3s/4s or other codeine products, and Dilaudid. Opioids also commonly tampered with by subjects (25.0% ≥ but < 50.0% subjects) included Percodan®, MS Contin®, and morphine products

Of 30 subjects, 13 subjects were included in the oral group, 9 subjects were included in the intranasal group, and 8 subjects were included in the intravenous group.

Subjects were not administered any drug products or involved in actually manipulating any products including Targiniq ER.

During the so-called "Treatment Phase" subjects were showed "standardized information cards, including photographs" for:

- Targiniq ER tablet
- Original OxyContin tablet
- Oxy IR tablet (immediate-release oxycodone
- Percocet tablet
- Percodan tablet
- Hypothetical oxycodone transdermal patch

The drug description contained standardized information including brand names, street names [if any], active ingredient, doses, solubility, potency, physical and pharmacologic properties, and release properties.

Subjects were given a few minutes to review the information, and the cards remained with the subjects as they completed the open-ended feedback, Opioid Attractiveness Scale, Value of Product Scale, and Likelihood to Tamper Scale. Once these assessments were completed for each product, the interviewer removed the information card and replaced it with the next opioid information card in the subject's randomized sequence, and so on, until all of the opioid products had been presented.

Subject assessments were documented using the following measures.

- Opioid Attractiveness Scale
- Value of Product Scale
- Likelihood to Tamper Scale
- VPS-LTS Index
- Overall Desirability Ranking
- Estimated Street Value

Results:

Based on the following concerns regarding the overall design of study ONU1009, this reviewer has elected not to consider the results of this study in the review of NDA 205777.

1. For each of the three cohorts (oral, intravenous, and intranasal) the number of subjects is small (8 to 13).
2. Subjects did not actually manipulate any products in the study.
3. Subjects were required to make their assessments based on looking at cards that contain photographs and selected information that could have produced a bias in the assessments.
4. Subjects did not have any exposure or manipulation experience for the type of formulation (opioid agonist combined with opioid antagonist) constituting Targiniq ER tablets.
5. There is no indication of the validity of the various assessment measures used in the study.
6. The Agency has not encouraged or endorsed the use of attractiveness studies in the assessment of abuse-deterrent formulations.

4.3 **Integrated assessment**

4.3.1 Evidence of abuse and misuse from scientific literature, external databases, and foreign marketing of product or substance

According to Sponsor, as of April 2013, oxycodone HCl/naloxone HCl controlled release tablets was approved in 36 countries under four different strengths depending on the specific country" 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg for twice daily administration.

At the time of the safety data cut-off date for NDA 205777 (December 2012) oxycodone HCl/naloxone HCl controlled release tablets was launched in 20 European countries and 9 non-European countries, with a total of approximately (b) (4) patient treatment days based on tablet sales. As of December 2012 the international drug safety database (manufacturer's AE reporting database: ARGUS) contained a total of 1874 unique cases involving a total of 3,956 adverse events. Thirty-one of these AEs were coded to be abuse or dependence-related preferred term. Eight of these cases involved attempts to manipulate the product for injection or insufflation resulting in withdrawal symptoms and requiring emergency attention. In the Integrated Summary of Safety, Sponsor provided descriptions of these incidences involving manipulation of oxycodone HCl/naloxone HCl controlled release tablets. They are provided verbatim below.

Case Narrative CAN-2010-0001610
Information on report reference number CAN-2010-0001610 was received on 18NOV2010 from a physician via a sales representative in Canada. This spontaneous report refers to a male consumer in his mid-20s. "The patient obtained Targin (controlled-release oxycodone/naloxone) from a friend and decided to crush it and snort/inject it. The patient was also routinely taking methadone. After taking the Targin (controlled-release oxycodone/naloxone), the patient felt uncomfortable and panicked. He called an ambulance and was rushed to the emergency room, very freaked out. His pupils were dilated. He was sweating, shaking, and feeling nausea. The patient was given fluids and observed overnight. He is now fine." Medical history, current conditions, and concomitant medications were not reported. Outcome was unknown for the events of drug dependence and drug abuse and recovered for the events of malaise, panic reaction, mydriasis, hyperhidrosis, tremor, and nausea. This case was rated serious due to the medical significance of drug dependence and drug abuse. Additional information has been requested. The case will be updated accordingly should more information become available.
***Follow up information was received on 06DEC2010 from the physician. The reaction abated after stopping Targin (controlled-release oxycodone/naloxone) and patient did not restart Targin (controlled-release oxycodone/naloxone). The event of drug dependence was removed from this case as the patient used Targin (controlled-release oxycodone/naloxone) only once. This case remained serious. No further information is expected.

Case Narrative USA-2012-0083153
Report reference number USA-2012-0083153 is a spontaneous report received on 01MAR2012 from a physician via a company representative at (b) (6) under local case number AU20120301-2 and was reported as follows: "Case Description: Report reference number AU20120301-2 was received on 01-Mar-2012 from a doctor in Australia. This spontaneous case refers to a male patient. It was reported that the patient injected Targin (oxycodone/naloxone controlled release tablets) that he had stolen from his father, and presented to hospital with pronounced opioid withdrawal symptoms. The patient was admitted for management. The patient's medical history included: history of opioid abuse/addiction. It is not known whether the patient was taking other medications. The reporting Health Care Professional believed the event to be definitely related to the suspect drug."
This case was rated to be serious due to the medical significance of the event drug abuse and involved hospitalization for the event pronounced opioid withdrawal symptoms. Further information is not expected.

Case Narrative USA-2012-0083943
Report reference number USA-2012-0083943 is a spontaneous report received on 15MAR2012 from a physician via a company representative at (b) (6) under local case number AU20120315-1, and was reported as follows: "Case Description: Report reference number AU20120315-1 was received on15-Mar-2012 from a healthcare professional in Australia, via a sales representative. This spontaneous case refers to a male patient. A female patient with chronic pain was prescribed Targin tablets, dose unknown. She gave a dose of Targin to her male partner, who crushed and injected it, and quickly went into severe withdrawal. The male was attended to and stabilized by paramedics. The reporting Health Care Professional did not consent to be contacted for further information, and did not provide a causality

assessment". This case was assessed as serious due to the medical significance of the event drug abuse. No further information is expected.

Case Narrative USA-2012-0084499
Report reference number USA-2012-0084499 is a spontaneous report received on 23MAR2012 from a health care professional via a company representative at (b) (6) under local case number AU20120323-3, and was reported as follows: "Case Description: Report reference number AU20120323-3 was received on 23-Mar-2012 from a healthcare professional in Australia via a sales representative. This spontaneous case refers to a male patient, aged 18-19 years old. On the (b) (6), two teenagers had obtained and filled a prescription for Targin (oxycodone/naloxone controlled release tablets) 20/10mg, allegedly for their father, who was in too much pain to present to the pharmacy and have the prescription dispensed. The pharmacist did notice aberrant behavior in the two teenagers as the male continued to walk in and out the pharmacy while the female continued discussions with the pharmacist. The pharmacist filled the prescription, and the teenagers left the pharmacy.
The following day police presented at the pharmacy and informed the pharmacist that the two teenagers had crushed Targin tablets and either administered it intranasally or parenterally, resulting in marked withdrawal. An ambulance had to be called and the two teenagers were taken to the emergency department of hospital. The gentleman whom they claimed to be their father was in fact their neighbor who was suffering from dementia, and whom they had defrauded $ (b) (6) from. The patient outcome was reported as recovered." The event of drug abuse was assessed as serious due to medical significance. No further information is expected.

Case Narrative USA-2012-0084501
Report reference number USA-2012-0084501 is a spontaneous report received on 23MAR2012 from a health care professional via a company representative at (b) (6) under local case number AU20120323-4, and was reported as follows: "Case Description: Report reference number AU20120323-4 was received on 23-Mar-2012 from a healthcare professional in Australia via a sales representative. This spontaneous case refers to a female patient, aged 18-19 years old. On the (b) (6), two teenagers had obtained and filled a prescription for Targin (oxycodone/naloxone controlled release tablets) 20/10mg, allegedly for their father, who was in too much pain to present to the pharmacy and have the prescription dispensed. The pharmacist did notice aberrant behavior in the two teenagers as the male continued to walk in and out the pharmacy while the female continued discussions with the pharmacist. The pharmacist filled the prescription, and the teenagers left the pharmacy. The following day police presented at the pharmacy and informed the pharmacist that the two teenagers had crushed Targin tablets and either administered it intranasally or parenterally, resulting in marked withdrawal. An ambulance had to be called and the two teenagers were taken to the emergency department of hospital. The gentleman whom they claimed to be their father was in fact their neighbor who was suffering from dementia, and whom they had defrauded $ (b) (6) from. The patient outcome was reported as recovered." The event of drug abuse was assessed as serious due to medical significance. No further information is expected

Case Narrative USA-2012-0085806
Report reference number USA-2012-0085806 is a spontaneous report received on 23APR2012 from a healthcare professional via a company representative at (b) (6)

(b) (6) under local case number AU20120423-2, and was reported as follows: "Case Description: Report reference number AU20120423-2 was received on 23-Apr-2012 from a healthcare professional in Australia. This spontaneous case refers to a female patient in her early thirties. The patient's medical history included: Unknown to ongoing Current On methadone programme. The patient's concomitant medications included the following: Effexor (venlafaxine). The patient injected (route not specified) Targin (oxycodone/naloxone controlled release tablets) dose 30/15mg (once only) on an unknown date in (b) (6). On an unknown date in (b) (6), an unknown interval after Targin (oxycodone/naloxone controlled release tablets) had been injected (drug abuse), the patient experienced opioid withdrawal, hallucinations, extreme agitation, aggression, incoherence, dyspnoea, and abdominal pain, necessitating hospitalization for (b) (6) days. Treatment included: sedation with midazolam, diazepam, morphine, clonazepam, and haloperidol. On an unknown date in (b) (6) the patient recovered.
The following information was provided:
"My client, aged (early 30.s) is on a methadone program here with me in (b) (6). Her only other therapy was Effexor 300mg. She injected 3 x Targin (10mg/5mg) and had (b) (6) days in hospital from (b) (6). On arrival by ambulance, she was hallucinating, extremely agitated, aggressive, incoherent, dyspnoeic and complaining of abdominal pain. She required sedation with Midazolam, Diazepam, Morphine, Clonazepam, and Haloperidol. She was admitted to the ward with a GCS score of 8 for airway management. She did not report any other drug use and a toxicology screen was not performed. A diagnosis of opioid withdrawal was made. She made a full recovery but her son was removed from her care. A diagnosis of Serotonin syndrome was not considered". The reporting Health Care Professional did not comment on the relatedness of the adverse events to the suspect drug. This case was rated to be serious as the opioid withdrawal, hallucinations, extreme agitation, aggression, incoherence, dyspnoea and abdominal pain involved hospitalization. No further information is expected."

Case Narrative USA-2012-0088398
Report reference number USA-2012-0088398is a spontaneous report received on 08JUN2012 from a pharmacist via a company representative at (b) (6) under local case number AU-2012-1060802, and was reported as follows: "Report reference number AU-2012-1060802 was received on 08-Jun-2012 from a pharmacist in Australia via a sales representative. This spontaneous case refers to a 40 year-old female patient. The patient's concomitant medications were not reported; it was reported that the patient had previously been on opiate replacement therapy. The patient injected Targin (oxycodone/naloxone controlled release) 20/10mg tablet and required ambulance assistance, hospitalization and police involved. The reporting pharmacist did not provide a causality assessment. This case was rated to be serious as the event involved hospitalization. No further information is available.

Case Narrative USA-2012-0091457
Report reference number USA-2012-0091457 is a spontaneous report received on 10AUG2012 from a physician via a company representative at (b) (6) under local case number AU-2012-1081001, and was reported as follows: "Case description: report reference number AU-2012-1081001 was received 10AUG2012 from a healthcare professional in Australia via a sales representative. The spontaneous case refers to a 47 year old male patient. The patient had been prescribed Targin (oxycodone/naloxone controlled-release tablets)

100/50mg daily (60/30mg in morning and 40/20mg at night) for chronic back pain. The patient was previously taking OxyContin (controlled-release oxycodone hydrochloride) 120mg daily prior to being prescribed Targin tablets. On (b) (6), the patient injected Targin (dose unknown) intravenously and experienced withdrawal. The patient attended the hospital emergency department due to the events. Treatment information was not provided. The patient recovered on an unknown date. Targin therapy was not prescribed to the patient again. The reporting healthcare professional did not provide a causality assessment." This case was assessed as serious due to the medical significance of event drug abuse. No further information is expected.

Sponsor also noted that in the ARGUS database were 216 cases containing an adverse event coded to a withdrawal-related preferred term or on the basis of containing ≥ 3 DSM IV-TR symptoms in the criteria for opioid withdrawal (19 cases of 216). According to Sponsor these cases were generally described as mild to moderate and transient in nature. Of the 216 cases, 121 involved withdrawal occurring after a patient was switched to oxycodone HCl/naloxone HCl controlled release therapy from other opioids, while 37 other cases involved withdrawal upon discontinuation or dose reduction of oxycodone HCl/naloxone HCl combination product. In 20 cases withdrawal was observed with patients were switched from oxycodone HCl/naloxone HCl combination product to a mono-ingredient oxycodone product.

4.3.2 Labeling issues

The language proposed under the heading of "In Vitro Testing" is Section 9.2 of the label is an accurate reflection of the results obtained in the in vitro studies. The principle emphasis is on the difficulty in separating out the naloxone HCl from the morphine sulfate with physical or chemical manipulation of Targiniq ER tablets.

The Sponsor has proposed to place under the heading of "Clinical Abuse Potential Studies" in Section 9.2 of label information on human abuse potential studies ONU1003 (intravenous and intranasal administration to non-dependent opioid experienced users) and ONU1008 (oral intact and chewed to opioid dependent (methadone-maintained subjects). This is acceptable.

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/s/

JAMES M TOLLIVER
06/24/2014

SILVIA N CALDERON
06/24/2014

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06/24/2014

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Pediatric and Maternal Health Staff Memorandum

Date: June 16, 2014 **Date Consulted:** May 16, 2014

From: Miriam Dinatale, D.O., Medical Officer
Pediatric and Maternal Health Staff

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

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

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

Drug: Targiniq ER (oxycodone hydrochloride / naloxone hydrochloride extended-release) tablets

NDA: 205777

Applicant: Purdue Pharma L.P.

Subject: Pregnancy and Lactation labeling

Materials Reviewed: NDA submission, Targiniq ER draft labeling, literature review

Consult Question:
"Is there specific language that should be added to the label regarding the effect of naloxone on the fetus or nursing infant?"

INTRODUCTION

On September 16, 2013, Purdue Pharma L.P. submitted a 505 (b)(2) new drug application (NDA) for Targiniq ER (oxycodone hydrochloride/naloxone hydrochloride extended release) tablets (NDA 205777), for the [redacted] pain [redacted], around-the-clock [redacted]. The sponsor proposes that the oxycodone component is intended to provide analgesia, and the naloxone component is intended as a deterrent for oxycodone abuse. The Referenced Listed Drugs (RLDs) are Narcan (naloxone hydrochloride), NDA 16636, OxyContin (oxycodone hydrochloride), NDA 20553, and reformulated OxyContin, NDA 22272. The OxyContin NDAs are Purdue Pharma L.P. products.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on May 16, 2014, to review and update the Pregnancy and Nursing Mothers information in the Targiniq ER labeling. PMHS-MHT performed a literature review of oxycodone and naloxone use in pregnancy and breastfeeding. This review summarizes available published data, and provides conclusions and recommendations regarding Pregnancy and Nursing Mothers labeling for Targiniq ER.

BACKGROUND

Oxycodone is a semisynthetic opioid analgesic with affinity for mu, kappa, and delta receptors in the brain, spinal cord and peripheral organs.[1] Opioid medications may be needed during pregnancy to manage severe pain associated with 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.[2]

Naloxone is a nonselective, competitive inhibitor of mu, kappa and delta-opioid receptors and displaces an opiate from the active site. It is used to treat opiate overdose and in Targiniq ER is being used to prevent the abuse of oxycodone, mainly when the tablet is crushed and used intranasally or intravenously, rather than orally, as intended. The American Academy of Pediatrics (AAP) recommends that naloxone not be administered directly to infants of narcotic-dependent mothers due to the risk of opioid withdrawal. Hale (2012) states that maternal naloxone use during lactation would be unlikely to cause adverse reactions in a breastfed infant since naloxone levels are low in breast milk levels and oral absorption of naloxone is minimal.[3]

REVIEW OF DATA

There are no data pertaining to pregnancy and lactation with the combination of oxycodone and naloxone at the 2:1 ratio seen with Targiniq ER. The data presented here are for studies with each individual drug.

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[1] Dunnmon, Preston. DCRP Consult Review NDA 205777. 3/17/2014.
[2] Sahin, Leyla. PMHS-MHT Review- Xartemis XR (NDA 204031). 10/28/2013
[3] Hale T. Medications and Mothers' Milk. 2012. Fifteenth Edition.

Literature Review of Oxycodone

Pregnancy

Two case-control studies[4] demonstrated statistically significant associations between opioid exposure in the first trimester of pregnancy and congenital malformations. A study done by the Center for Disease Control (CDC) and the National Birth Defects Prevention Study (NBDPS) showed a positive association between oxycodone use and pulmonary valve stenosis seen in eight cases (OR 2.4, 1.1-5.4).[5] A study done by the Slone Epidemiology Center Birth Defects Study (BDS) showed a positive association between opioid use and spina bifida in 10 cases (OR 2.5, 1.3-5.0).[6]

Reviewer comments: Oxycodone was previously reviewed by MHT on October 28, 2013, and the literature references and comments for this review mirror those in that memo.[7] The ability to draw clear conclusions about the teratogenic risk of opioids from these studies is limited because of the following factors: recall bias (interviews with some mothers were conducted up to three years after giving birth), the small number of exposed cases, and the lack of adjustment for multiple statistical analysis, which may result in chance finding.

There are also several studies that have not shown an increase in congenital malformations following first trimester exposure to oxycodone. The following studies are listed below:

- A case control study based on five cases exposed to oxycodone[8]
- A prospective observational study of 78 women who were exposed to oxycodone[9]
- The National Institutes of Health Collaborative Perinatal Project, a case control study of 58,282 mother-child pairs, which included eight women exposed to oxycodone[10]

In animal reproduction studies, orally administered oxycodone showed no effect on fertility or early embryonic development in the rat at the highest dose tested (8 mg/kg/day). Oxycodone was not teratogenic when orally administered to rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. In a prenatal and postnatal development study in rats there was decreased mean body weight for F1 pups during lactation and the early post-weaning phase in the highest dose group (6 mg/kg/day). However, body weight of the pups recovered during the later post-weaning phase. There were no other effects on the development of the F1 pups, with regard to their survival, physical development, behavior or reproductive performance.[11]

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[4] These case control studies were conducted in the U.S. by the Center for Disease Control (CDC), the National Birth Defects Prevention study (NBDPS), and the Slone Epidemiology Center Birth Defects Study (BDS).

[5] Broussard C, Rasmussen S, Reefhuis J et al Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics Gynecology. 2011; 204: 314.

[6] 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.

[7] Sahin, Leyla. PMHS-MHT Review- Xartemis XR (NDA 204031). 10/28/2013.

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

[9] 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.

[10] 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.

[11] Purdue Pharma L.P. Nonclinical Overview. NDA 205777, Targiniq, 9/16/2013

Reviewer comments: Overall, there are limited human data on the teratogenic risk of oxycodone exposure during pregnancy. At this time it is not possible to draw any clear conclusions regarding the risk of malformations following oxycodone exposure during pregnancy.[12]

<u>Lactation</u>

The Drugs and Lactation Database (LactMed)[13] was searched for available lactation data on the use of oxycodone. 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. 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: In this study, the active metabolites of oxycodone (noroxycodone and oxymorphone) were not measured. Oxycodone has an oral bioavailability of 60% to 87% in adults. Noroxycodone is the major circulating metabolite with an area under the curve (AUC) of 0.6 relative to that of Oxycodone. Oxymorphone is present in the plasma only in low concentrations.[14] *While the estimated infant exposure was 8% of the maternal weight-adjusted dosage of oxycodone, the lack of data on the level of active metabolite may have provided an underestimation of the drug in breastmilk. Also, only colostrum was analyzed, which may not provide an accurate measure of drug in mature milk. Hale (2012) reports if the relative infant dose of a maternally used drug is less than 10%, then generally, the drug is safe to use during lactation.*[15]

In another study, 50 breastfeeding mothers, who delivered by cesarean section, received oxycodone. Maternal plasma and colostrum samples were analyzed for oxycodone at 24 hour intervals (24, 48 and 72 hours postpartum without respect to the time of the previous oxycodone dose). The most common doses received by the mothers during the previous 24 hours were 60 mg, 40 mg, and 20 mg. Mean colostrum concentrations at the 3 collection times were 58 mcg/L (range 7 to130 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 times higher than maternal serum levels. Five women had detectable oxycodone in milk 37 hours

[12] Sahin, Leyla. PMHS-MHT Review- Xartemis XR (NDA 204031). 10/28/2013

[13] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[14] www.drugs.com/pro/oxycodone html

[15] Hale T. Medications and Mothers' Milk. 2012. Fifteenth Edition.

after the last dose. Forty-one infants had 45 blood samples taken at 48 hours. Only one of the samples had a detectable (>2 mcg/L) oxycodone level of 7.4 mcg/L.[16]

Reviewer comments: Oxycodone was detectable in the breastmilk of five women 37 hours after the last dose. However, the study did not analyze the milk samples at peak times (1-2 hours post-dose). This may have caused underestimation of peak drug level in breastmilk. Another concern is that the concentrations of oxycodone in colostrum were 3.2 to 3.4 higher than maternal serum levels. This may be due to oxycodone accumulating in the breastmilk and having a different rate of clearance from the maternal plasma.

In a retrospective study, the rate of CNS depression in breastfeeding infants was compared between three cohorts of 533 breastfeeding mother-infant pairs exposed to oxycodone (n=139), codeine (n=210), or acetaminophen only (n=184). Nursing mothers were contacted by telephone to determine the degree of maternally perceived central nervous system (CNS) depression in their infants. 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.[17]

There is a case report of a breastfeeding newborn infant with 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.[18]

Literature Review of Naloxone

Pregnancy

In a retrospective chart review, ten opioid-dependent pregnant women were treated with buprenorphine and naloxone between January 2010 and June 2011. Seven maternal outcomes were measured including: weight gain, fetal presentation at delivery, Cesarean section, analgesia during delivery, urine drug screening results at delivery, number of days of maternal hospital stay and whether or not breastfeeding was started following delivery. Eleven neonatal outcomes were measured as well and included: gestational age at delivery, 1-and 5-minute Apgar scores, head circumference, length and weight at birth, treated for

[16] 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 JObstet Gynaecol. 2007; 47:181-5.

[17] Lam J, Kelly L, Ciszkowski 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

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

neonatal abstinence syndrome (NAS), total amount of morphine sulfate needed to treat NAS, length of hospital stay for NAS treat, and length of hospital stay. In this study, four neonates out of ten were treated for NAS (no criteria for diagnosis was noted in this article), which, according to the authors, was comparable to that seen in other buprenorphine reviews (40% in this study vs. 52% seen in other buprenorphine reviews). The limitations of the study that the authors noted included the following: a small sample size, no comparison group, the study is retrospective, and it did not allow for examination of birth defects.[19]

In another study, retrospective analyses on maternal and neonatal outcomes were collected from seven previously published studies examining treatment for opioid-dependent pregnant women. In this review there were no significant adverse maternal or neonatal outcomes related to the use of buprenorphine and naloxone for the treatment of opioid dependence during pregnancy compared to using buprenorphine alone, methadone, or methadone-assisted withdrawal.[20]

In a controlled study evaluating the effect on naloxone on fetal behavior, 54 healthy pregnant women between 37 and 39 weeks gestation were given either 0.4 mg of naloxone IV or an equal amount of saline. The women then underwent cardiotocographic or echographic examinations at the same time each day and in the same position. The following fetal activities were evaluated: gross fetal body movement, fetal eye movements, fetal breathing and fetal heart rate. There was an increase in fetal heart rate accelerations, fetal body movements and fetal breathing movements after naloxone administration, especially in the first hour. There was also an increase in active sleep and active awake states in the naloxone group compared to the control. The authors concluded that the reversal of the effects of fetal endorphins by naloxone could be involved in the modulation of fetal behavior.[21]

In animal reproduction studies, orally administered naloxone revealed no effect on fertility or early embryonic development in the rat at the highest dose tested (800 mg/kg/day). Orally administered naloxone was not teratogenic in the rat or rabbit at the maximum doses tested (800 mg/kg/day and 400 mg/kg/day, respectively). In a prenatal and postnatal development study in rats naloxone at the highest dose (800 mg/kg/day) produced mortality and significant toxicity in maternal rats and resulted in increased pup deaths in the immediate postpartum period. However, in surviving pups, no effects on development or behavior were observed.[22]

Lactation

The Drugs and Lactation Database (LactMed) was searched for available lactation data on the use of naloxone. There is no information on the presence of naloxone in breastmilk. However, there is the potential for withdrawal symptoms in a young breastfed infant. In

[19] Debelak, K, Morrone, W, O'Grady, K, Jones, H. "Buprenorphine + Naloxone in the Treatment of Opioid Dependence during Pregnancy- Initial Care and Outcome Data." The American Journal on Addictions. 2013; 22: 252-254.

[20] Lund et al. "A Comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes." Substance Abuse, 2013; 7:61-74.

[21] Arduini, D, Rizzo, G, Dell'Acqua, S, Mancuso, S, Romanini, C. Effect of naloxone on fetal behavior near term. American Journal of Obstetrics & Gynecology. 1987: 156; 474-478.

[22] Purdue Pharma L.P. Nonclinical Overview. NDA 205777, Targiniq, 9/16/2013

adults, the majority, but not all of a given dose of naloxone, will be inactivated following oral administration. If a small amount of naloxone is transferred from the breast milk to the infant, there is a chance that naloxone will be orally absorbed by the infant. Because of the infant's immature blood-brain barrier, this may cause withdrawal symptoms. The American Academy of Pediatrics (AAP) recommends that naloxone not be administered directly to infants of narcotic-dependent mothers due to the risk of opioid withdrawal. Hale (2012) notes that maternal naloxone use during lactation would be unlikely to cause adverse reactions in a breastfed infant since naloxone levels are low in breast milk levels and oral absorption of naloxone is minimal.[23]

Reviewer Comment: Although Hale (2012) classifies breastfeeding as moderately safe with maternal use of naloxone, the classification was based on the use of the product in an overdose situation, not on the potential daily, around-the-clock maternal use as would be the case with the use of this product.

DISCUSSION
PREGNANCY AND NURSING MOTHERS LABELING

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 label 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. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. 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 human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

Pregnancy

The cumulative data on oxycodone and naloxone 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 and naloxone during pregnancy.

[23] Hale T. Medications and Mothers' Milk. 2012. Fifteenth Edition.

Lactation
In one study oxycodone persisted in breast milk up to 37 hours after the last dose. In neonates the clearance rate of oxycodone varies significantly.[24] 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. The studies that have been done on oxycodone have failed to collect data on oxycodone's active metabolites (noroxycodone and oxymorphone). In addition there are no data on oxycodone drug levels in milk after the first 72 hours when colostrum is replaced by transitional and then mature milk, which makes it difficult to accurately quantify the levels of oxycodone in human milk. PMHS-MHT concurs with the American Academy of Pediatrics Committee on Drugs not recommending oxycodone use in the lactating mother.[25] Infant withdrawal is an additional potential concern with naloxone use in a lactating woman.

CONCLUSIONS
A pregnancy category C is the appropriate classification for Targiniq ER labeling due lack of adequate studies in pregnant women, the potential for fetal withdrawal, and findings from available animal reproduction data[26] (see 21 CFR 201.57 (c)(9)(i)(A)(3)). The pregnancy subsection of Targiniq ER labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of Targiniq ER labeling was revised to comply with current labeling recommendations, as well as incorporating the breast feeding benefit/risk statement from the proposed PLLR.

LABELING RECOMMENDATIONS
PMHS-MHT reviewed existing labeling for oxycodone and naloxone to make labeling consistent across products. In addition, PMHS-MHT collaborated with the Pharmacology/Toxicology reviewer in structuring 8.1 Pregnancy and recommends the following revision to the Pregnancy and Nursing Mothers subsections of Targiniq ER labeling. Final labeling will be negotiated with DAAAP and may not fully reflect changes suggested here. See Appendix A for the applicant's proposed Targiniq ER labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME
Prolonged use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3)

[24] Pokela ML, Anttila E, Seppala T et al. Marked variation in oxycodone pharmacokinetics in infants. Paediatr Anaesth. 2005; 15:560-5.
[25] Sachs HC. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on selected topics. Pediatrics 2013;132(3).
[26] Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans."

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm; may precipitate fetal withdrawal. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug depending on importance of drug to mother. (8.3)

FULL PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME

Prolonged maternal use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)].*

5 WARNINGS AND PRECAUTIONS

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TARGINIQ ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid-withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with TARGINIQ ER in pregnant women. The naloxone component of TARGINIQ ER may precipitate opioid withdrawal in a fetus due to the immaturity of the fetal blood-brain barrier. Animal reproduction studies were not conducted with the combination of oxycodone and naloxone, the components of TARGINIQ ER. However, animal data are available from studies conducted with the individual components. Embryo-fetal toxicity was not observed following oral administration of oxycodone to rats and rabbits during the period of organogenesis at doses equal to or 30 times, respectively, the maximum recommended human dose (MRHD) of 80/40 mg/day of TARGINIQ ER. Decreased pup weight was observed in rats with oral administration of oxycodone throughout pregnancy at doses 0.8 times the MRHD of 80/40 mg/day of TARGINIQ ER. Embryo-fetal toxicity was not observed following oral administration of naloxone to pregnant rats and rabbits during organogenesis at doses 192 times the MRHD of

80/40 mg/day of TARGINIQ ER. TARGINIQ ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies, regardless of drug exposure, have a background risk of 2-4% for major birth defects, and 15-20% for pregnancy loss.

Clinical Considerations

Fetal/Neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[*see *Warnings and Precautions (5.3)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. TARGINIQ ER 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 opioid antagonist, such as naloxone, must be available for reversal of narcotic-opioid induced respiratory depression in the neonate.

Data

Animal data

No evidence of fetal harm was observed after oral doses of oxycodone in rats as high as 8 mg/kg/day or as high as 125 mg/kg/day in rabbits, which, on a body surface area basis (60 kg person) were approximately equal to or 30-times, respectively, the oxycodone intake at the maximum recommended dose of 80/40 mg/day of TARGINIQ ER. Similarly, orally administered naloxone was not teratogenic in the rat or rabbit at the maximum dosages tested (800 mg/kg/day or 400 mg/kg/day, respectively) which were equivalent to approximately 192-times the intake of naloxone at the maximum recommended dose of 80/40 mg/day of TARGINIQ ER.

In a peri-/postnatal development study with oxycodone in rats, there was decreased mean body weight of pups during lactation and the early post-weaning phase at the highest dosage tested (6 mg/kg/day; equivalent to 0.8-times the oxycodone intake at the maximum recommended daily dose of TARGINIQ ER on a body surface area basis). However, body weight of the pups recovered during the post-weaning phase. There were no other effects on the development of the pups or their survival, physical development, behavior, or reproductive performance.

In a peri-/post-natal development study with naloxone in rats, the highest dosage of 800 mg/kg/day (equivalent on a body surface area basis to approximately 192-times the intake of naloxone at the maximum recommended dose of 80/40 mg/day of TARGINIQ ER) produced mortality and significant toxicity in maternal rats, which was associated with increased pup deaths in the immediate postpartum period. However, in surviving pups, no effects on development or behavior were observed. Mild toxic signs were also observed in maternal

rats that received 200 mg/kg/day (approximately 48-times the intake of naloxone at the maximum recommended daily dose of TARGINIQ ER on a body surface area basis); however, there were no adverse effects on the pups.

8.3 Nursing Mothers

The oxycodone component of TARGINIQ ER is likely present in breast milk because oxycodone when given as a single agent is present in breast milk. It is unknown whether naloxone is present in breast milk. Instruct patients not to undertake nursing while receiving TARGINIQ ER. Do not initiate TARGINIQ ER therapy in a nursing woman because of the possibility of sedation or respiratory depression in an infant.

Withdrawal signs can occur in breast fed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped. Furthermore, naloxone may precipitate opioid withdrawal in a breastfed infant.

17 PATIENT COUNSELING INFORMATION

Neonatal Opioid Withdrawal Syndrome

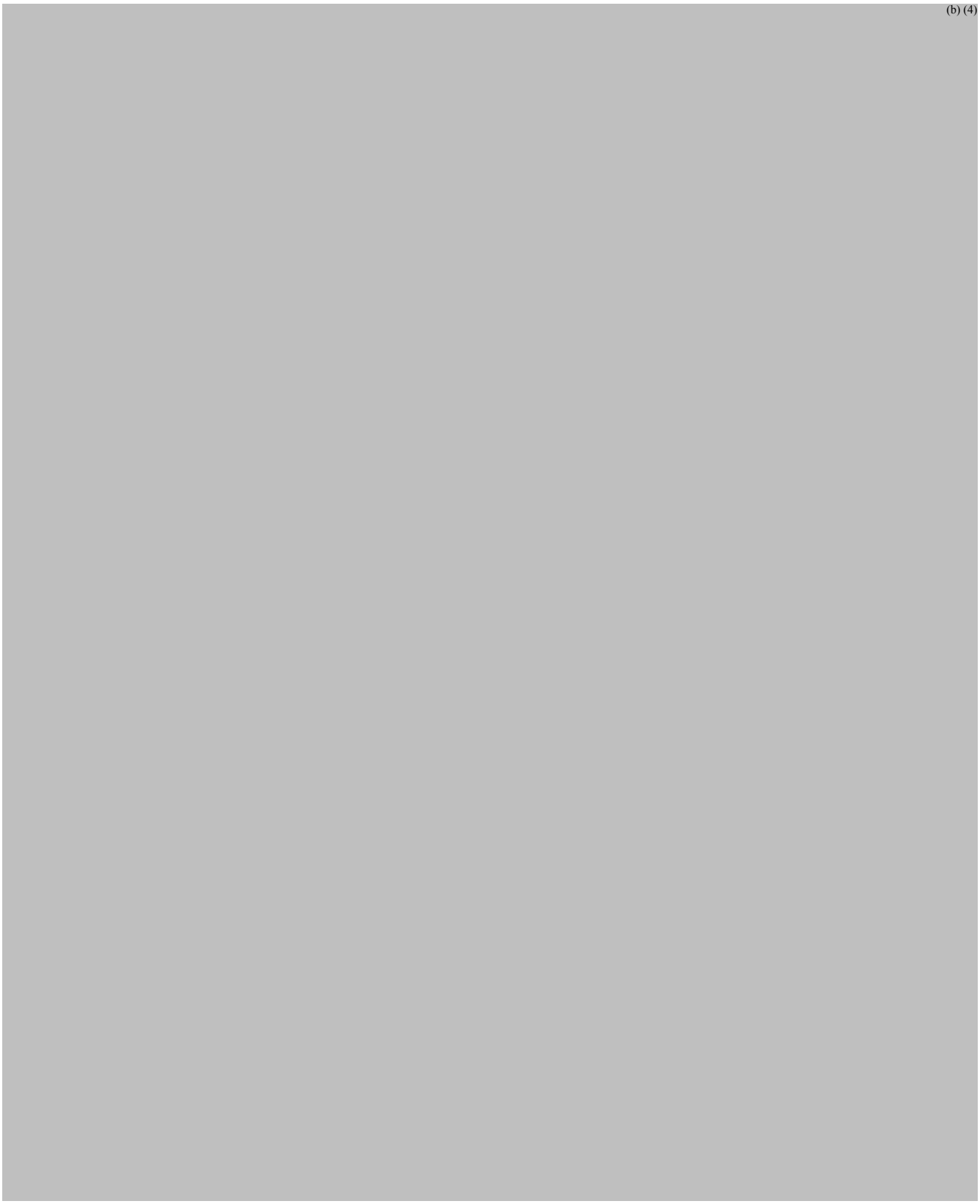
Inform female patients of reproductive potential that prolonged use of TARGINIQ ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[*see *Warnings and Precautions (5.3)]*.

Pregnancy

Advise female patients that TARGINIQ ER can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

APPENDIX A- Applicant's proposed Targiniq ER labeling

(b) (4)



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

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

/s/

MIRIAM C DINATALE
06/17/2014

JEANINE A BEST
06/17/2014

LYNNE P YAO
06/20/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 9, 2014

TO: Elizabeth M. Kilgore, M.D., Medical Officer
Ellen W. Fields, M.D., M.P.H, Clinical Team Leader
Lisa E. Basham, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D. for Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205777

APPLICANT: Purdue Pharma L.P.

DRUG: oxycodone HCl/naloxone HCl controlled release tablets

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Management of (b) (4) pain (b) (4) clock (b) (4)

CONSULTATION REQUEST DATE: November 8, 2013
CLINICAL INSPECTION SUMMARY GOAL DATE: June 9, 2014
DIVISION ACTION GOAL DATE: July 23, 2014
PDUFA DATE: July 23, 2014

I. BACKGROUND

Purdue Pharma L.P. (Purdue) is seeking approval for the fixed combination OXN (oxycodone HCl and naloxone HCl [and naloxone-3-glucuronide]) for the management of (b) (4) pain (b) (4), around-the-clock (b) (4) The basis for approval of the proposed indication of this NDA is the pivotal study ONU3701 entitled "A Randomized, Double-blind, Placebo-controlled, Multicenter Trial with an Enriched Study Design to Assess the Efficacy and Safety of Oxycodone/Naloxone Controlled-release Tablets (OXN) Compared to Placebo in Opioid-experienced Subjects with Moderate to Severe Pain due to Chronic Low Back Pain who Require Around-the-clock Opioid Therapy".

In study ONU3701, there were 1924 subjects who were screened and 1109 subjects qualified for the open-label titration phase (14 subsequently did not enter). There were 601 subjects who completed the open-label phase and 600 of these subjects were randomized. There were 399 subjects who completed the study. The first subject was enrolled on May 25, 2011 and the last subject completed the study on October 15, 2012. (b) (4)

This study was conducted at 132 sites in the United States. Sites were chosen based on enrollment. Two of the three sites initially selected had recently been inspected (b) (4) for other applications. Both inspections were VAI. Therefore, two alternative sites were chosen.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 205777 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol ONU3701 # of Subjects Randomized	Inspection Date	Final Classification *Pending
Eduardo Almaguer Site 2066A-4526	14 subjects	1/08- 17/2014	VAI
Armen Arslanian Site 0609A-4532	13 subjects	2/24- 4/2/2014	VAI

Jeffrey Potts Site 1210A-3500	36 subjects	1/15- 22/2014	NAI
[redacted] (b) (4)			

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in Form FDA 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Eduardo Almaguer, M.D.
760 East 49th Street
Hialeah, FL 33013

a. What was inspected: The inspection covered IRB submissions and approvals, the regulatory binder, training, credentials, subject selection criteria, informed consents, drug accountability, adverse event reporting, 1572s, financial disclosure statements, and monitor/sponsor audit activities, as well as information maintained in the subject source data and case reports. There were 19 subject records reviewed. Subject's e-diary was not consistently printed, and therefore only review of select data was possible. The firm was not provided a copy of the CRF or subjects' e-diaries.

b. General observations/commentary: There were 19 subjects screened and 14 subjects were randomized. The IRB of record was [redacted] (b) (4) IRB. The site had no standard operating procedures (SOPs); the site has been doing clinical research since 2003. Records were paper with data then transcribed to the case report forms. All subjects met inclusion/exclusion criteria. There was no under-reporting of adverse events. Comparison of the source data and the data line listings did not reveal any major deficiencies. Drug accountability review found no discrepancies. For some subjects, select CRF/e-diary summary print-outs were found intermingled with the source data; the CRF/e-diary data was verified against the source data when it was available.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued for the following deficiency:

OBSERVATION 1
An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, the "Site Signature and Duty Delegation Log" originally permitted the Principle Investigator (PI), Sub-Investigator (Sub-I) and Clinical Research Coordinators (CRCs) the authority to perform "Investigational Product Dispensing". The current log has this duty crossed out for the CRCs. There is no initial/date or equivalent notation indicating when and who made the adjustment to the log. Source data revealed that CRCs have dispensed investigational product throughout the study (from the first through the last subject).

OSI Reviewer Comment: Dr. Almaguer responded with a Note to File explaining that the task was crossed out by mistake. He and the sub-investigator assigned the doses of investigational product and the CRCs dispensed. A call was made to the Supervisor, Florida Board of Medicine. According to the Supervisor, only licensed and registered physicians and physician's assistants can dispense controlled substances in the state of Florida. This law also applied to controlled substance dispensing for clinical research studies in Florida.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although a regulatory violation was noted as described above, it does not significantly impact primary safety and efficacy analyses. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

2. Armen H. Arslanian, M.D.
45 Pearl Street
Brockton, MA 02301-2858

a. What was inspected: Records reviewed were informed consents, IRB approvals and communications, monitoring logs, delegation logs, enrollment logs, Sponsor correspondence, 1572s, adverse event reports, subject e-diary entries, drug accountability and source documents. There were 35 subject records reviewed.

b. General observations/commentary: There were 35 subjects screened and 13 subjects randomized. The first subject was screened at the study site on 11/30/2011. The date of last follow-up for any study subject was on 09/18/2012. There were 24 subjects initially enrolled in the open label portion of the study. Data listings show 23 subjects because Subject #005 entered the open label phase but did not have an e-diary entry showing administration of study drug.

The IRB used by the study site for this study was (b) (4) IRB. Correspondence showed Dr. Arslanian submitted a continuing review application in a timely manner. SAE's and unanticipated problems were reported to the IRB.

The study site had a CD with the subjects' e-diary entries on them. During

review of source documentation and comparing data listings, it was noted that the e-diary entries by the subjects are direct reflections of the data within the data listings. During drug accountability review, it was noted that subjects would enter in their e-diary that they took study drug doses. However, progress notes and drug accountability records show the subject did not take the study drug. Sponsor/CRO instructions were that for e-diary errors, site staff was told that subject entries could not be changed. Only administrative changes could be made (wrong date was displayed, PI should change any dose level increase, etc.).

The primary endpoint for this study was the "average pain over the last 24 hours" (on an 11-point scale) obtained at Visits 5 through 8 and the unscheduled study drug discontinuation visit (if applicable). The primary outcome for the efficacy analysis was the "average pain over the last 24 hours" score at Week 12 of the double-blind period. Because all e-diary entries are direct reflections of the data listings, all "average pain over the last 24 hours" entries made by the subjects for Visits 5 through 8 matched the data listings. The primary efficacy endpoint was verifiable.

Adverse events were reviewed. There was some under-reporting of adverse events. There were no outside medical records noted during review of subject records; all medical history appeared to be reported verbally by the subject and recorded in the subject source records.

A discrepancy in delegated tasks was noted. The Laboratory Technician (LT) took vital signs from subjects, for example, Subject #032 on 06/07/2012. According to the Site Signature and Duty Delegation Log, LT is not delegated to take vital signs. This was considered by PI to be an oversight and LT should have been listed on the Site Signature and Duty Delegation Log with the responsibility of trial measurements. The Site Signature and Duty Delegation Log also list responsibility #12 Clinical Opiate Withdrawal Scale (COWS) as being performed by a physician only. It was noted that the RN and CRC, conducted COWS assessments. Initial protocol and protocol amendment #1 states the investigator will conduct the COWS assessments. Protocol amendment #2 changed the wording to medically qualified personnel, including nurses. Protocol amendment #1 and amendment #2 were IRB approved on 08/23/2011, prior to subject screening. Therefore, amendment #2 was in effect prior to first subject screening and enrollment and allows for the RN to conduct the COWS. The Site Signature and Delegation Duty Log were not updated to reflect the change for COWS assessment responsibility.

Source documents were kept within binders. The binders were organized and in good condition. During review of records, discrepancies were found within some source records. For example, Subject #003 Visit 2.1 progress note initially refers to the subject as "her" even though Subject #003 is male. Subject #012 Progress note for Visit 4 states ECG's were reviewed; however, per study

design, ECG's are not collected at Visit 4 and Subject #012 did not have ECG's taken at Visit 4.

At the end of the inspection, a four item Form FDA 483 Inspectional Observations was issued with the following observations:

OBSERVATION 1
Investigational drug disposition records are not adequate with respect to quantity and use by subjects.

Specifically, study drug and rescue drug disposition records for quantity dispensed, quantity returned used, and quantity returned unused, are discrepant, and source documentation does not contain explanations for the discrepancies. Examples include but are not limited to:

- Subject #032 was dispensed Level 60 OXN 30mg/15mg on 05/24/2012 and 05/31/2012. As per Open Label Blister Cards for dose level 60, there are two tablets per dose (total 4 tabs per day).The labels state there are OXN 10mg/5mg 20 tablets and OXN 20mg/10mg 20 tablets for a total of 40 tablets within each blister card. The corresponding entries on Subject #032's drug accountability log for 05/24/2012 and 05/31/2012 show the subject was only dispensed 20 tablets at each visit. These entries on the accountability log are inaccurate as the subject was dispensed 40 tabs each visit, not 20 tabs. Subject e-diary reflects the subject took 24 tablets and should have taken 28 tablets. There are no explanations within source records stating these discrepancies and the accountability log is inaccurate. The accountability log is also inaccurate in stating only eight tablets were returned used or quantity ingested by subject. Per e-diary, the subject took 24 tablets; this would leave 4 unaccounted for. The four unaccounted for tablets are not listed on the accountability log.
- Similar discrepancies occurred for Subject #024, including only documenting 20 tabs were dispensed instead of 40 tablets on the accountability log for Level 60 tabs and progress notes that do not state discrepancies between e-diary and amount of study drug returned (i.e., 5 tablets unaccounted for between 5/08-15/2012). Progress notes also do not thoroughly describe discrepancies of study drug taken by subject versus amount returned by subject.
- Subject #025 Visit 3 Taper Blister Card Level 40 contains 28 tablets. There are discrepancies between e-diary entries, accountability log, progress notes and worksheets for Subject #025 between Visits 3 (4 tablets unaccounted for), Visit 4 (6 tablets unaccounted for), and Visit 8 (Early Discontinuation). Progress notes do not give thorough explanation of discrepancies with drug accountability.

OSI Reviewer Comment: Protocol Section 9.5.3 "Drug Accountability" states the investigator and study staff will be responsible for the accountability of all

clinical supplies (dispensing, inventory, and record keeping). The amount of study drug reported used/ingested by the subject was to be ascertained through subject report in their e-diary and/or verbal report if there is a discrepancy between actual counts and e-diary accounting. There was to be documentation of any and all information regarding discrepancies, investigation into discrepancies, as well as information sought and found should be thoroughly documented in the subjects' source. Dr. Arslanian acknowledged the discrepancies and has instituted corrective actions, including a site SOP on diary compliance. The SOP also requires that the Director of Operations perform source binder quality assurance.

OBSERVATION 2
Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation

Specifically, per the e-diary manual, if the study dose changes during the Titration period, then the investigator must modify the subject's dosage in the e-diary. Subjects were titrated to higher dose levels; however, the e-diary was not changed to the higher dose level. Examples include but are not limited to:

- Subject #003 was titrated to 20mg/10mg from 12/16/2011 through 12/22/2011 and e-diary entries during this Open-label timeframe show 10mg/5mg. Subject #003 was titrated back down to 10/5 mg on 12/22/2011.
- Subject #004 was titrated to 20mg/10mg on 12/21/2011 and to 30mg/15mg on 12/28/2011 and subsequent to both dates, e-diary entries throughout Open-label period show 10mg/5mg.
- Subject #024 was titrated to 30mg/15mg on 05/08/2012 and subsequent e-diary entries throughout Open-label and Double-blind periods show 20mg/10mg.
- Subject #032 was titrated to 30mg/15mg on 05/24/2012 and subsequent e-diary entries throughout Open-label and Double-blind periods show 20mg/10mg.
- Subject #034 was titrated to 20mg/10mg on 06/05/2012 and subsequent e-diary entries throughout Open-label and Double-blind periods show 10mg/5mg.

OSI Reviewer Comment: The e-diary manual states that, if the subject's study dose changes during the Titration period, then the investigator must logon and select 'Adjust settings' and modify the subject's dosage. Although the study dose changes in the e-diary were not changed, the correct doses were entered into the IVR system for all subjects. Dr. Arslanian acknowledged the discrepancies. In the future, all subject doses will be reviewed against the subject electronic diary at every visit and adjusted accordingly.

OBSERVATION 3
An investigation was not conducted in accordance with the signed statement of investigator and investigational plan

Specifically,

a) Protocol ONU370 Section 9.3.4 Double-blind Entry Criteria states in order to enter the double-blind period, the subject must achieve a stable and effective dose of OXN. The following subjects did not meet the criteria for achieving a stable and effective dose of OXN and were entered into the double blind period on the following dates:

- Subject #024 on 05/15/2012
- Subject #032 on 06/07/2012
- Subject #034 on 06/12/2012

*OSI Reviewer Comment: **Subject #024** does not have an e-diary entry for 05/09/2012. Subject #024 source documentation does not accurately state drug accountability and does not record that there was a discrepancy/missed dose on 05/09/2012, so it is unclear whether Subject #024 took study drug on 05/09/2012. Dr. Arslanian acknowledged the discrepancies but stated in his written response that, after conducting onsite drug accountability, he confirmed that the subject was on the same dose for seven consecutive days. **Subject #032** does not have e-diary entries for 06/04/2012 and 06/01/2012. Source documentation does not document the "average pain over the last 24 hours" score for the missing e-diary data on 06/04/2012 (one of the last three days). The dates listed on the worksheet for the seven consecutive days are not seven consecutive days. Dr. Arslanian acknowledged the discrepancies but stated in his written response that, after conducting onsite drug accountability, he confirmed that the subject was on the same dose for seven consecutive days. **Subject #034** does not have an e-diary entry for 06/10/2012. Source documentation does not document the "average pain over the last 24 hours" score for the missing e-diary data on 06/10/2012 (one of the last three days). Source documents for Subject #034 do not thoroughly document an explanation of the drug accountability discrepancy of the missing e-diary entry on 06/10/2012. Dr. Arslanian acknowledged the discrepancies but stated in his written response that, after conducting onsite drug accountability, he confirmed that the subject was on the same dose for seven consecutive days.*

Dr. Arslanian stated that any deviation in the future will be discussed with the Sponsor's Medical Monitor and clearly documented in the subject's source documents. This is included in a new SOP for administering informed consent.

b) Protocol ONU370 Section 9.4.1.2.2 Visit 2 (Open-label Titration Period) states study center staff will review diary data daily and contact the subjects at least twice a week to assess efficacy, safety, tolerability, and study drug compliance. There is no documentation to show subject diary

data was being reviewed daily by study center staff.

OSI Reviewer Comment: The study site had access to the online program TrialMax. The study site could log on with a password and review real time subject e-diary results. Site staff stated the study site reviewed these daily; however, there is no documentation to prove this. The print dates of the TrialMax printouts were all done the day of or the day before a study visit (for example, Subject #032 was scheduled for the randomization visit on 06/07/2012 and the TrialMax printout was printed on 06/07/2012).

Dr. Arslanian acknowledged the observation but stated that the online portal was reviewed but not documented accordingly. In the future, all site diary reviewers will be documented via a note in the subject's source record. Documents will also undergo QA. This reflects the procedures in the new SOP on quality assurance.

c) Protocol ONU370 Exclusion Criteria #18 states subjects with a positive result on urine drug testing for illicit drugs at Visit 1 will be excluded
- Subject #005 Visit 1 central laboratory results dated (b) (6) show the urine was positive for illicit drugs (Cocaine Metabolite). Subject #005 participated in and was given Open-label study drug at Visit 2 on 12/14/2011. Dr. Arslanian signed Subject #005's positive Cocaine laboratory results on 12/20/2011, (b) (6) days after the report was generated.

OSI Reviewer Comment: Subject #005 showed up at the study site and had a titration failure visit conducted on 01/04/2012. Subject #005 reported he was incarcerated from 12/15/2011 until 01/04/2012 and stated while incarcerated his room was broken into and all study medication that was dispensed to him was stolen. The site did report this to the IRB and Sponsor. Dr. Arslanian acknowledged the observation and a new SOP for central lab results has been revised to incorporate the use of a lab tracker, which tracks the date each specimen is shipped out and the date lab results are received. All labs will be reviewed by the first available investigator in a timely manner.

d) Protocol ONU370 Protocol Section 9.4.1.2.2, Visit 1 (Screening Period) states the investigator/medically qualified designee will review the subject's laboratory results and ECG results upon receipt. Visit 1 laboratory results and ECG results were not reviewed by the investigator/medically qualified designee upon receipt. (For example, Subject #012, Subject #005, Subject #034, Subject #020)

OSI Reviewer Comment: Dr. Arslanian stated that all the labs and ECGs were reviewed by him or a sub-PI and that it appears that signed copies were inadvertently destroyed. In the future, all labs will be reviewed by the first available investigator in a timely manner.

OBSERVATION 4
Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests.

Specifically, informed consent form Version 2, dated 06/21/2011, includes a form for subjects to choose whether they want to participate in the Pharmacogenomic sub-study. Three subjects chose to decline the Pharmacogenomic sub-study. Pharmacogenomic blood samples were drawn from these three subjects.

- Subject #023 signed ICF 04/05/2012 and had sample drawn on 05/29/2012
- Subject #025 signed ICF 04/17/2012 and had sample drawn on 04/17/2012
- Subject #031 signed ICF 04/25/2012 and had sample drawn on 09/05/2012

OSI Reviewer Comment: It was confirmed during the inspection that all samples were destroyed. Dr. Arslanian stated that in the future there will be ongoing QA of the ICFs in real time.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they do not significantly impact primary safety and efficacy analyses. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

3. Jeffrey A. Potts, M.D.
200 South Wenona Street
Suite 170
Bay City, MI 48706

a. What was inspected: The inspection included reviews of the informed consent process, protocol compliance, 1572s, training and experience, CVs, delegation of responsibilities, financial disclosures, sponsor/monitoring correspondence, test article accountability and source document verification. There were 20 subject records reviewed.

b. General observations/commentary: There were 97 subjects screened and 36 subjects randomized. The original PI was Dr. Russell Struble (FEI: 3007984340). Dr. Potts was a sub-investigator and was named PI after Dr. Struble moved out of the state in February 2012. (b) (4) IRB was the IRB of record. IRB approval for replacing Dr. Struble as the PI was granted on 2/10/12 and the informed consent was amended to reflect the PI change.

The site files were contained within individual manila folders. The files were

found to be complete, legible, and organized. Associated medical records were filed in the study files. After enrollment it did appear the site and PI managed suspected diversions appropriately. There was no evidence of subjects enrolling at other sites. Source data was verifiable regarding eligibility, efficacy endpoints, adverse events, randomization, investigational drug accountability, concomitant medications, and protocol compliance. There was no evidence of under-reporting and the primary efficacy endpoint was verifiable.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were a few discussion points:

- The source documents lacked adequate documentation of adverse event follow-up.
- Two subjects had concomitant medications listed that were not reported (Celexa and Soma- they were not exclusionary).

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. (b) (6)

a. **What was inspected:** An attempt was made to exam study records at the last known site location for Dr. (b) (6). An internet search of public records was also conducted. Dr. (b) (6) had been placed on hold by the Sponsor after routine monitoring uncovered a number of inconsistencies, including drug dispensation anomalies, limited study oversight, lack of documented training and experience of staff, lack of source documentation for patients and informed consent violations. This site was subsequently removed from the study following allegations that the investigator was involved in writing prescriptions to illegally provide drugs for abuse. (b) (6) but the Sponsor and CRO (PPLP/ (b) (4)) were not immediately made aware of the allegations. Federal criminal charges were filed against Dr. (b) (6) for conspiracy to distribute drugs outside the scope of legitimate medical practice. PPLP/ (b) (4) became aware of the allegations on (b) (6) during an audit of the site. The audit had numerous findings and the site had also failed to report the indictment charges to (b) (4) IRB. Thus, the decision was made to exclude all data from this site from the analyses.

Since enrollment in the (b) (6) study was closed at the time of the findings, the site was not actively screening subjects for the study so site closure for

protocol non-adherence as well as the indictment was not necessary. A routine Close-Out Visit for Dr. (b) (6) site due to study completion was conducted on (b) (6). On or about (b) (6), Dr. (b) (6) pled guilty to one felony count of conspiring to knowingly, intentionally acquire or obtain controlled substances by misrepresentation, fraud or deception.

b. **General observations/commentary:** The FDA field investigator visited the last known business address of Dr. (b) (6) (as noted above). It was a vacant office building with a "For Rent" sign on the side of the building. The FDA field investigator attempted to contact the phone number of the business and got a recording saying that the number was discontinued. The FDA field investigator then visited a post office at (b) (6) staff stated that there was no forwarding address for Dr. (b) (6).

The inspection of public records via an internet search revealed a letter to Dr. (b) (6) suspending his medical license after he pleaded guilty to one felony count.

(b) (6)

c. **Assessment of data integrity:** The firm is out of business. Data from this site should not be used. File referred to the Office of Enforcement.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic sites. (b) (4) .

Observations noted above for Drs. Almaguer, Arslanian and Potts are based on the preliminary review of the Establishment Inspection Reports. An inspection summary addendum will be

generated if conclusions change upon OSI final classification.

Two of the clinical sites inspected, Dr. Almaguer and Dr. Arslanian, were each issued a Form FDA 483 citing inspectional observations and classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for both sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Data from these sites is acceptable for use in support of the indication for this application.

Dr. Potts was not issued a Form FDA 483; the classification of the inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.

Although an audit of Dr. (b) (6) site was not possible, information obtained by the FDA field investigator confirmed the communications from the Sponsor. Data from this site are not considered reliable.

In general, based on the inspection of the three clinical sites, the inspectional findings of these sites support validity of data as reported by the Sponsor under this NDA.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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

/s/

CYNTHIA F KLEPPINGER
06/09/2014

SUSAN LEIBENHAUT
06/09/2014

KASSA AYALEW
06/09/2014

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 # 205777 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Targiniq ER Established/Proper Name: Oxycodone Hydrochloride/Naloxone Hydrochloride Dosage Form: tablet Strengths: 10/5, 20/10, 40/20 mg		
Applicant: Purdue Pharma L.P. Agent for Applicant (if applicable):		
Date of Application: 9/23/13 Date of Receipt: 9/23/13 Date clock started after UN:		
PDUFA Goal Date: 7/23/14	Action Goal Date (if different):	
Filing Date: 11/22/13	Date of Filing Meeting: 10/28/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Management of (b) (4) pain (b) (4), around-the-clock (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***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.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 070851

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	☐	☒		Requested corrections to IND and NDA
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)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
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)].**	☐	☒	☐	
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)]?** ***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***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☐	

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☐	☒		Requested in AK letter. Submitted 10/30/13.

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*: 10/17/13	☒	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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*	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	Cardio-Renal

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 11/18/10 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9/13/12 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		Written responses were provided to questions re: Phase 3 study on 8/19/11

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/28/13

BLA/NDA/Supp #: 205777

PROPRIETARY NAME: Targiniq ER

ESTABLISHED/PROPER NAME: Oxycodone HCl/Naloxone HCl

DOSAGE FORM/STRENGTH: Extended-Release Tablets, 10/5 mg, 20/10 mg, 40/20 mg

APPLICANT: Purdue Pharma L.P.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	
	CPMS/TL:	Parinda Jani	
Cross-Discipline Team Leader (CDTL)	Ellen Fields		
Clinical	Reviewer:	Elizabeth Kilgore	
	TL:	Ellen Fields	
~~Social Scientist Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OTC Labeling Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Clinical Microbiology (*for antimicrobial products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———

Clinical Pharmacology	Reviewer:	Srikanth Nallani	
	TL:	Yun Xu	
Biostatistics	Reviewer:	Feng Li	
	TL:	Janice Derr	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Belinda Hayes	
	TL:	Dan Mellon	
Statistics (carcinogenicity)	Reviewer:	Steven Thompson	
	TL:	Karl Lin	
~~Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
Product Quality (CMC)	Reviewer:	Julia Pinto	
	TL:	Prasad Peri	
~~Quality Microbiology *(for sterile products)*~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
CMC Labeling Review	Reviewer:	Julia Pinto	
	TL:	Prasad Peri	
Facility Review/Inspection	Reviewer:	Cynthia Kleppinger	
	TL:		
OSE/DMEPA (proprietary name & C&C)	Reviewer:	Vicky Borders-Hempsill	
	TL:	Morgan Walker	
OSE/DRISK (REMS)	Reviewer:	Jamie Wilkins Parker	
	TL:	Reema Mehta	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Juandria Williams	
	TL:		

~~Bioresearch Monitoring (OSI)~~	~~Reviewer:~~	~~———~~	~~———~~
	~~TL:~~	~~———~~	~~———~~
Controlled Substance Staff (CSS)	Reviewer:	Jim Tolliver	
	TL:	Silvia Calderon	
Other reviewers	OPDP: Eunice Chung-Davies Biopharm: Sandra Suarez/Tapash Ghosh		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO PK bridge to OxyContin and Narcan
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**: Joint review issue with Pharm/Tox. MDD limit unsupported. Impurity specification inadequate.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**: CII	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: request for calrification on randomization in Study ONU3701	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: MDD issue – see comment under clinical	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Req. CoAs for drug substances and test for moisture content	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: TBD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter (This label is an ER/LA label and will benefit from SEALD's input on the class of labels. Upon approval of the class, Purdue will update this label)
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	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]
☐	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.

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

/s/

LISA E BASHAM
05/06/2014

Date: April 7, 2014

From: Preston M. Dunnmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

Through: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

To: Brian K. Strongin, RPM
Division of Gastroenterology and Inborn Errors Products

Subject: CV safety of opioid receptor antagonists, impressions from prior DCRP consults

Relevant Prior Consults and Product Labels:

- DCRP Consult – Alvimopan/Entereg (Nov 2008)
- DCRP Consult – Methylnaltrexone (MTXN)/Relistor (Jun 2012)
- DCRP Consult – (b) (4)
- DCRP Consult – Oxycodone+Naloxone/Targiniq ER (Mar 2014)
- Entereg Label
- Relistor Label

Summary Findings – Alvimopan/Entereg (oral)

DCRP evaluated the safety data that were available at the time our Division was consulted on the four opioid receptor antagonists noted above. Concern for the CV safety of these drugs was initially raised from opioid-induced bowel dysfunction (OBD) experience with alvimopan. Specifically, for alvimopan,

- There were six controlled phase 2/3 studies of OBD in which 1728 subjects without cancer were administered 0.5 or 1.0 mg Entereg twice daily (i.e., the dose of Entereg was much lower than in the post-operative ileus (POI) trials) and 790 were administered placebo for up to one year; except for study SB-767905/14, the studies lasted 12 weeks or less.
- Cardiovascular AEs were neither a prespecified safety endpoint nor prospectively adjudicated and follow-up of dropouts was limited so ascertainment of their occurrence is unlikely to be complete and may not be accurate (though blinded data were not likely to have been biased in this regard).
- In study SB-767905/14 538 non-cancer subjects with OBD were randomized to 0.5 mg Entereg twice daily and 267 to placebo. Seven MIs and three episodes of unstable angina were observed in subjects administered Entereg and none in subjects administered placebo.
- No significant differences in the prevalence of risk factors for cardiovascular disease between the two treatment groups were observed; the prevalence of risk

factors was higher in the enrolled population than in the general American population.

- In the other shorter duration controlled phase 2/3 studies of OBD no imbalance in cardiovascular risks were observed; one MI and one episode of unstable angina were observed in subjects exposed to Entereg and 3 MIs and one episode of angina unstable angina were observed in placebo subjects.

Alvimopan was ultimately approved with a boxed warning for short-term use (15 doses) in an in-patient setting (via ETASU REMS). No CV safety study was performed.

Summary Findings – Methylnaltrexone (MNTX)/Relistor (subcutaneous injection)

Relistor is approved for the treatment of opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. It was noted at the time of this approval that use of Relistor beyond four months had not been studied. The recommended dose is weight based: 8-12 mg SQ qD or QoD.

Approval was subsequently sought for a new indication – the treatment of OIC in patients with chronic non-cancer pain. In support of this application, two studies were submitted (studies 3356 and 3358). Cardiovascular AEs in these trials were neither a prespecified safety endpoint nor prospectively adjudicated and follow-up of dropouts was limited, so ascertainment of their occurrence is unlikely to be complete and may not be accurate (though the four weeks of blinded data from study 3356 were not likely to have been biased in this regard).

Only study 3356 encompassed controlled and blinded data, and only for four weeks. The remaining 8 weeks of study 3356 was open-label, uncontrolled, PRN dosing. Dropouts during the 4-week double-blind phase of study 3356 were approximately two times more frequent in the Relistor arms as compared to the placebo arm. CV adverse events reported during both phases of this trial were small in number, as seen in the table below, and there were no deaths (source: review Division's NDA review):

CV events of interest reported by investigators in study 3356 safety pop

4 wk double-blind phase			
Preferred term	**MNTX 12 mg Q D N = 150**	**MNTX 12 mg QOD N = 148**	**Placebo N = 162**
chest pain	0	1	0
musculoskeletal chest pain	0	0	1
hypertension	0	0	1
8 wk open-label phase			
	MNTX 12 mg prn N = 364		
hot flush	1		
hyperhidrosis	1		
hypertension	2		

chest discomfort	1		
dyspnea	1		

Study 3358 was open-label and uncontrolled, enrolling 1040 across 120 centers in 6 countries (US, Australia, Spain, Korea, and Colombia), with a follow-up of 48 weeks. Multiple CV adverse events occurred during the 48-week uncontrolled follow-up period of this trial as shown in the table below (source: review Division's NDA review):

Table: CV events of interest reported by investigators in study 3358 in all-subjects population (source, review Division's NDA review)

Preferred term	MNTX 12 mg prn N = 1034 n (%)
cerebrovascular accident	1 (0.1)
cardiac arrest	1 (0.1)
sudden death	1 (0.1)
myocardial infarction	4 (0.4)
cardiac failure congestive	1 (0.1)
coronary artery disease	2 (0.2)
in-stent coronary artery stenosis	1 (0.1)
angina pectoris	3 (0.3)
angina unstable	1 (0.1)
prinzmetal angina	1 (0.1)
chest pain	1 (0.1)
non-cardiac chest pain	5 (0.5)
hyperhidrosis	2 (0.2)
hypertension	2 (0.2)
hypotension	3 (0.3)
chest discomfort	3 (0.3)
dyspnea	4 (0.4)
palpitations	1 (0.1)
electrocardiogram QT prolonged	5 (0.5)
Atrioventricular block second degree	1 (0.1)
electrocardiogram PR prolongation	1 (0.1)
heart rate decreased	2 (0.2)
drug withdrawal syndrome	2 (0.2)

Because of the dearth of controlled clinical trial data for MTXN and the lack of an interpretable number of reported CV adverse events in the 4-week controlled phase of study 3356, an attempt was made to examine the temporal relationship between MNTX dosing and CV adverse events that were reported for the uncontrolled data from both study 3356 and study 3358. Multiple cases were noted where CV and/or withdrawal-type symptoms occurred in proximity to MTXN dosing.

(b) (4)

Salix appealed this request citing the fact that MTXN has been administered to thousands of patients with advanced illnesses receiving palliative care, and that the company disagreed with the premises that MTXN can cause withdrawal symptoms in some patients, that withdrawal symptoms may be accompanied by hemodynamic changes that increase myocardial oxygen demand, and that their small datasets were not sufficient to characterize the CV safety profile of MNTX adequately.

Summary Findings – (b) (4)

The phase 3 development program for (b) (4) was more extensive, was composed of substantially more controlled data, and was more robustly analyzed. Specifically, in the (b) (4)

A graphical representation of the patients contributing to the Phase III integrated safety analysis is shown in the figure below (from the sponsor's ISS, page 16):

(b) (4)

All serious CV events (and selected non-serious CV AEs of interest) occurring in the Phase 3 clinical studies of (b) (4) were adjudicated by an independent external CV event adjudication committee (CV-EAC). In addition, to support assessment of potential

cardiac risks, serial digitized ECGs were collected (in triplicate) 2 hours after administration of the first dose of (b) (4) to correlate with (b) (4) Tmax and at all subsequent study visits, and were read centrally. Patients were also observed for changes in blood pressure (BP) and pulse 1 hour after administration of the first dose of (b) (4) (as well as at the end of the 4-hour post-first-dose observation period). The process for selecting CV events for adjudication was as follows:

- The Investigator was to report all deaths and pre-specified MACE, as well as any other events deemed by the Investigator to be appropriate for adjudication.
- (b) (4):
    - Reported all CV SAEs
    - Performed a medical review to identify non-serious cases that might have been missed by the Investigators and sent a query to the Investigator concerning appropriateness for adjudication; in such cases, (b) (4) reserved the right to report an event to the CV-EAC even if the Investigator did not consider it appropriate for adjudication..

DCRP reviewed the CV safety information available from this development program, noting some of the same design weaknesses as were present in the other development programs, as follows:

- Clinical trials not designed for CV event ascertainment
- Patients who prematurely withdrew were not followed through to the end of the studies
- Approximately (b) (4) of patients withdrew prematurely from the 12-week data pool.

That being said, DCRP's assessment was that there is no definitive CV safety signal from (b) (4) preclinical data, ECG data and TQT study, clinical vital sign data (changes in SBP, DBP, and HR), or MACE outcomes (stoke, MI, CV death, hospitalization for unstable angina, hospitalization for CHF). Indeed, adjudicated MACE outcomes from the Phase 3 trials were as follows (sponsor table 15):

Table 15 Number (%) of patients with ≥1 CV outcome event during the treatment period or post-treatment follow-up as determined by the independent CV-EAC (placebo-controlled pool and Study (b) (4)

Category	Placebo-controlled pool			(b) (4)-week safety study	
	Placebo	(b) (4)		Usual care	(b) (4)
Patients with any AE submitted to the CV-EAC[a]	7 (1.6)	12 (2.7)	13 (2.9)	11 (4.1)	11 (2.1)
Number of AEs submitted[a]	11	17	15	12	13
Any MACE per CV-EAC	**2 (0.5)**	**2 (0.5)**	**1 (0.2)**	**2 (0.7)**	**2 (0.4)**
CV death	0	2 (0.5)	0	1 (0.4)	1 (0.2)
Acute MI	2 (0.5)	1 (0.2)	1 (0.2)[b]	0	1 (0.2)
Stroke	0	0	0	1 (0.4)	0
Other CV events of interest per CV-EAC					
Hospitalization for unstable angina	0	0	0	0	0
Hospitalization for heart failure	0	0	1 (0.2)	1 (0.4)	0

[a] Deaths due to any cause, serious CV AEs, and selected non-serious CV AEs were adjudicated by the independent external CV-EAC, as described in Section 1.1.4.1.

[b] (b) (4)

AE Adverse event; CV Cardiovascular; CV-EAC Cardiovascular Event Adjudication Committee; MACE Major adverse cardiovascular event; MI Myocardial infarction; (b) (4)

Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.5; and Module 5.3.5.2, (b) (4) clinical study report, Table 11.3.6.1.2.

From this table, the MACE rates per 100 patient-years of exposure in the placebo-controlled trials (b) (4)

It was noted, however, that of the seven deaths that occurred in the entire program (b) (4), only five of the seven were from non-pulmonary embolus cardiovascular causes. Four of these five subjects were taking (b) (4) and three of these five subjects, all who had taken (b) (4), experienced acute myocardial infarctions that resulted in death. However, given how few events there were, any causal relationship is unclear.

CV adverse events occurred more frequently on (b) (4) at either dose tested in subjects experiencing both a CV adverse event and a GI adverse event in the 12-week controlled pivotal studies (b) (4) (0.5%, 1.6%, and 1.8% respectively for placebo, (b) (4). However, looking at these cases, most were non-serious reports of hypotension, hypertension, palpitations, or hot flashes/flushing. (b) (4) patient experienced

angina twice, and [redacted] patient experienced extrasystoles. This trend was seen once again in the data for study [redacted] where all [redacted] patients experiencing a GI AE and a CV AE were taking [redacted] of these patients experienced a pericardial effusion [redacted] developed AFib, however the remainder involved flushing and hypertension. Taken together, these results suggest that while withdrawal can be associated with CV adverse events, none of those documented involved ischemic catastrophes in these rather small studies.

Summary Findings – Oxycodone+Naloxone/Targiniq ER (OXN)

The data structure of this submission was large and complex, involving both patients with cancer and non-cancer pain, placebo controlled studies, active comparator studies, and open-label follow-up studies. Accordingly, the data structure of the integrated safety database is shown in the table below (from the sponsor's ECVE):

Table 2: Integrated Analysis Groups for Cardiovascular Analysis

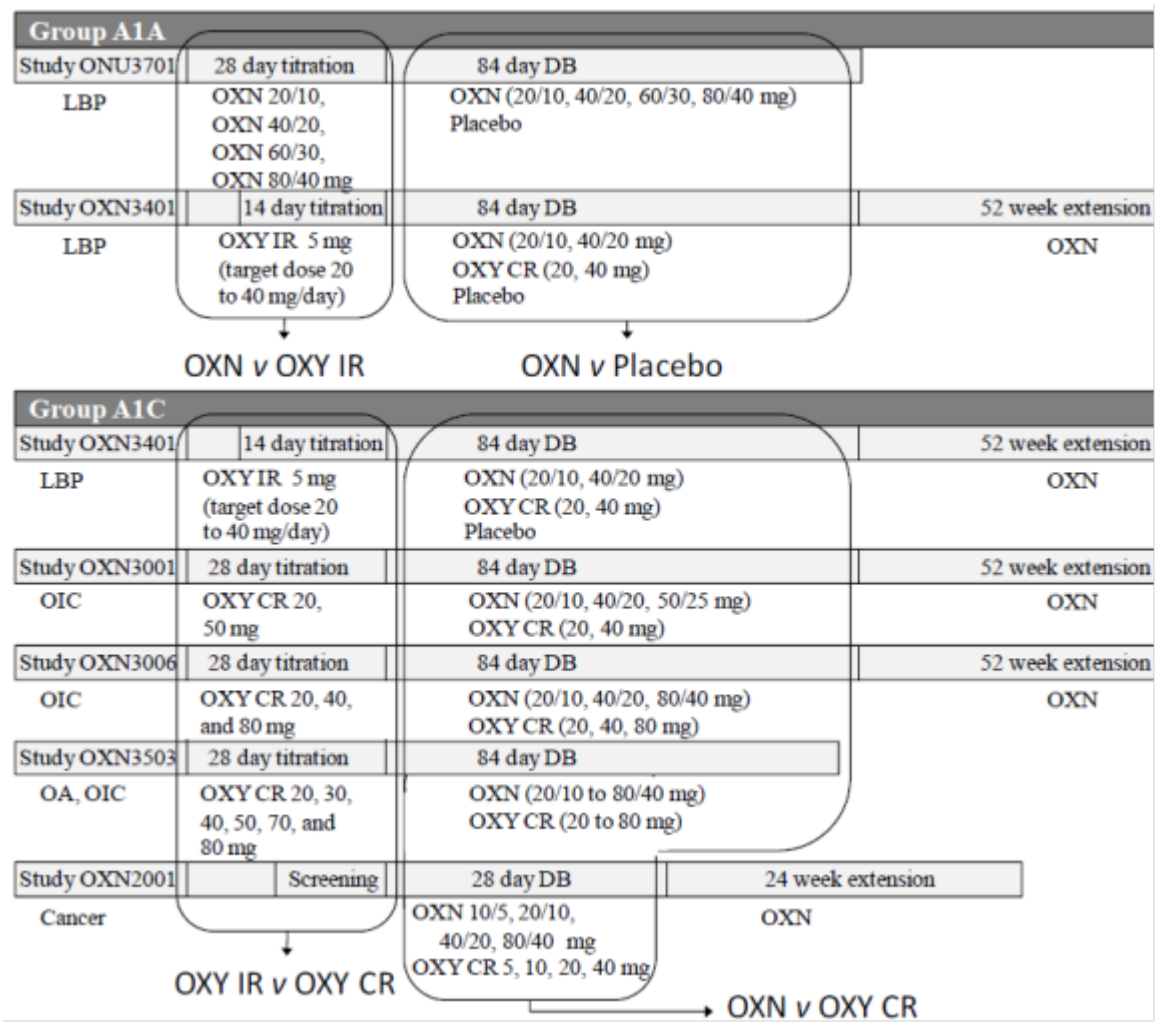
Analysis group/ Period analyzed	Studies included
Group A1A Titration Double-blind Double-blind + extension	Placebo-controlled studies involving subjects with nonmalignant chronic pain (2 studies): ONU3701, OXN3401
Group A1C = A1B[a] + OXN2001 Titration Double-blind Double-blind + extension	OXY CR-controlled studies involving subjects with nonmalignant pain and malignant chronic pain (5 studies): OXN3001, OXN3006, OXN3401, OXN3503, OXN2001
Group A1D = A1B[a] + OXN2001 + ONU3701 Titration + double-blind + extension	Studies to compare OXY (OXY CR and OXY IR) and OXN over the longest continuous period of time possible. Subjects who received different treatments during the titration, double-blind, or extension periods are excluded from these analyses (see Table 3) (6 studies) : ONU3701, OXN3001, OXN3006, OXN3401, OXN3503, OXN2001
Group C Overall (titration, double-blind, extension)	Studies in chronic pain, healthy subjects, abuse liability, and in special populations and situations (29 studies): All studies defined in Group A1A and A1C, including the open-label titration and open-label extension period data. Phase 1 studies involving healthy subjects: ONU1001, ONU1002, ONU1009, OXN1003, OXN1004, OXN1005, OXN1008, OXN1009, OXN1011, OXN1013, OXN1016, OXN1018, OXN1403, OXN1505, OXN1506 Studies of abuse deterrence and other special populations and situations: ONU1003, ONU1004, ONU1007, ONU1008, OXN1006, OXN1007 and OXN1017 Active medication-controlled phase 4 study in nonmalignant cancer pain: OXN4502 Note that only studies also included in groups A1A and A1C provide long-term data.

Though high level information for all OXN-treated was considered (Group C), DCRP's review focused on the controlled data from:

- Group A1A – the placebo-controlled trials in subjects with nonmalignant chronic pain
    - 2 placebo-controlled randomized phase 3 studies (ONU3701 and OXN3401)
    - Study ONU3701 utilized a blinded opioid taper during the first 2 to 10 days of the double-blind period for the subjects assigned to the placebo group, depending on the OXN dose at randomization.
    - Study OXN3401 did not utilize an opioid taper during the double-blind period; rather subjects underwent an opioid taper period prior to open-label titration to exclude those demonstrating excessive signs or symptoms of opioid withdrawal.
    - The data from the open-label titration periods in this pool are displayed by treatment (OXY IR in study OXN3401 and OXN in study ONU3701) and are presented separately from the data collected in the double-blind and open-label extension periods.

- Group A1C – the OXY-CR-controlled trials in subjects with nonmalignant chronic pain and malignant chronic pain
    - 5 OXY CR-controlled randomized phase 2 and 3 studies (OXN2001, OXN3001, OXN3006, OXN3401, and OXN3503)
    - no OXN treatment was used during the open-label titration period in this pool
    - The data from the open-label titration periods in this pool are displayed by treatment (OXY IR or OXY CR) and are displayed separately from the data collected in the double-blind and open-label extension periods.

The designs of the trials incorporated into those two Groupings are given in the figure below:



Overall (all pooled studies, Group C), a total of 3073 subjects were exposed to total daily doses of OXN ranging from 10/5 mg to > 100/50 mg.

For the placebo controlled trials (Group A1A),

- A total of 1680 subjects received at least 1 dose of study drug during the open-label titration period. Of the 1680 subjects, 1095 subjects (study ONU3701 only) received OXN and 585 subjects (study OXN3401 only) received OXY IR. The subject-years of exposure were higher in the OXN group (55 subject-years) compared with the OXY IR group (23 subject-years), primarily because of the higher number of subjects treated with OXN during titration and protocol differences (from ECVE Table 13, not shown).
- During the double-blind period, a total of 911 subjects received at least 1 dose of study drug (ECVE Table 14, below). Of the 911 subjects, 451 subjects received OXN and 460 subjects received placebo. The subject-years of exposure were slightly higher in the OXN group (86 subject-years) compared with placebo (79 subject-years).

- A total of 379 subjects received at least 1 dose of OXN during the open-label extension.

For the active-control trials (Group A1C),

- A total of 1707 subjects received at least 1 dose of study drug during the open-label titration period. Of the 1707 subjects, 1122 subjects received OXY CR and 585 subjects received OXY IR. The subject-years of exposure were higher in the OXY CR group (47 subject-years) compared with the OXY IR group (23 subject-years), primarily because of the higher number of subjects treated with OXY CR during titration.
- During the double-blind period, a total of 1284 subjects received at least 1 dose of study drug (Table 16). Of the 1284 subjects, 638 subjects received OXN and 646 subjects received OXY CR. The mean cumulative duration and the subject-years of exposure were similar for the OXN and OXY CR treatment groups. A total of 970 subjects received at least 1 dose of OXN during the open-label extension; a total of 1177 subjects received OXN during the double-blind and open-label extension periods.

Though the integrated safety dataset for this program was expansive, the following limitations for ascertaining and assessing CV events were noted:

- Distinct populations – with the A1C population being older, including malignant pain, and other non-back pain conditions
- Distinct run-in protocols – with placebo controlled trials (Group A1A) including an OXN run-in arm for which there was a staggering 45.1% premature discontinuation rate. Ninety-five of the 494 patients who dropped out prematurely during the run-in (19%) dropped out due to adverse events. It is unclear how many of these patients dropped out before having a follow-up ECG (QTc analyses were only performed on study 3701 patients who had one post-baseline ECG). Extracting these 494 patients during the run-in essentially "sanitized" the results of the Group A1A double-blind safety data because only patients tolerant to OXN during the run-in were randomized. Of note, from the Group A1A run-in, 3 subjects (0.5%) in the OXY IR group and 20 subjects (1.8%) in the OXN group experienced at least 1 SMQ-based CV AE.
- The stat plan states that only in trial 3701 were patients who prematurely discontinued study drug encouraged to stay in the trial for follow-up until the end of the trial. All other patients were censored following premature withdrawal. Indeed, the sponsor states the following during their analysis of concomitant withdrawal and CV adverse events: *"Since the proportion of censored observations was high (> 95%), the wide CI reflects more uncertainty."*
- Multiple small studies with different dosing algorithms, run-ins, and follow-up schedules have been integrated. None were sized or powered to assess CV outcomes, and ascertainment of CV events was undoubtedly sub-optimal. Evidence for this ascertainment limitation includes but is not limited to the retrospective reclassification of premature withdrawal reasons by the Discontinuation Reason Adjudication Committee (DRAC), the relatively small

number of CV events that were recorded, and the fact that assessment of CV safety was the objective of none of these trials.

- Given the relative high baseline CV risk of the trial populations, especially the Group A1C population, CV events could reasonably have been expected to occur. The small number of CV events that were recorded was undoubtedly effected by the short duration of the trials themselves, the very large dropout rates in these trials (run-in and double-blind phases), the large percentage of censored observations (and so I assume censored observation days), as well as the challenges noted for ascertainment even before censoring.

With these limitations in mind, DCRP noted the following:

- MACE events were more frequent in the comparator arms as compared to the OXN treatment arms of both pooled GroupA1A (placebo controlled trials) and Group A1C (OXY CR-controlled trials), as shown in the following summary table (from the sponsor's ECVE):

Table 17: Summary of Incidence Rate and Relative Risk of FDA-Defined Custom Major Adverse Cardiac Events, SMQ-Based Major Adverse Cardiac Events, SMQ-Based Cardiovascular Serious Adverse Events, and SMQ-Based Cardiovascular Adverse Events During the Double-Blind Period, Randomized Safety Population

Group A1A	Placebo N = 460 n (Rate)	OXN N = 451 n (Rate)	Relative Risk[a]	95% CI	*P*-value
At least 1 FDA cMACE	2 (2.3)	0	-	-	-
At least 1 SMQ-based MACE[b]	2 (2.3)	0	-	-	-
At least 1 SMQ-based CV SAE	2 (2.3)	4 (4.2)	1.85	(0.35, 9.83)	0.4727
At least 1 SMQ-based CV AE	18 (20.3)	20 (20.8)	1.03	(0.58, 1.81)	0.9310
Group A1C	**OXY CR N = 646 n (Rate)**	**OXN N = 638 n (Rate)**	**Relative Risk[a]**	**95% CI**	***P*-value**
At least 1 FDA cMACE	3 (2.4)	1 (0.8)	0.34	(0.04, 3.22)	0.3464
At least 1 SMQ-based MACE[b]	5 (3.9)	2 (1.6)	0.41	(0.08, 2.06)	0.2773
At least 1 SMQ-based CV SAE	8 (6.3)	9 (7.2)	1.15	(0.46, 2.87)	0.7728
At least 1 SMQ-based CV AE	48 (37.7)	44 (35.1)	0.93	(0.67, 1.29)	0.6775

- Exposure-corrected non-MACE cardiovascular adverse event rates were similar between OXN and comparator-treated patients. These observations are limited by the very high percentages of antecedent dropouts in the run-in periods, a high censoring rate of premature withdrawals, sub-optimal CV event ascertainment in all trials, and the brief duration of follow-up in these short studies.

- No signals for excess MACE, non-MACE CV AEs, or repolarization/conduction system toxicity with OXN were identified from these studies.

- OXN appears to be associated with elevations of both SBP and DBP in patients previously treated (presumably for hypertension, and hypertensive AEs occurred. Of the nine patients experiencing an SMQ-based CV AE and opioid withdrawal symptoms in the overall population (Group C) during any study period, three of the nine experienced blood pressure elevations in close proximity to OXN dosing, one of which was a hypertensive crisis. There were no concomitant AEs involving BP elevation with withdrawal symptoms in any comparator group.

- Though the number of subjects in which a CV AE/SAE occurred within 28 days of withdrawal symptoms was small, the hazard ratio for the time to first CV SAE was 14 times higher in patients with opioid withdrawal symptoms within 28 days (p=0.0006), and 5 times higher for the time to first non-serious CV AE in patients with opioid withdrawal symptoms within 28 days (p=0.0014), regardless of treatment.

Overall Assessment

From a mechanistic point of view, CV adverse event observations for these drugs should be interpreted in the context of an understanding of the determinants of myocardial oxygen demand. Opioid withdrawal (be that central or peripheral in the GI tract) induces physiologic stress in some patients. This physiologic stress will increase myocardial work and myocardial oxygen demand. Any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease. Indeed, in the evaluation of safety for such products, patients with these conditions are not "confounders" – they are exactly the patients that would be expected to have difficulties with these physiologic stressors. These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important.

In addition to those physiologic stressors that can be associated with opioid withdrawal in some patients, there are at least three other mechanisms by which CV adverse outcomes could theoretically occur with these agents:

1. Syndromes of increased vasomotor tone. Peripherally, this would include elevations of systemic blood pressure. In the coronary circulation, the concern would be drug-induced epicardial coronary vasospasm with classic Prinzmetal's angina. This is more than a hypothetical concern. Opioid antagonists (including the more mu-specific molecules) induce contraction of the intestinal smooth muscle (peristalsis). If this same effect were to occur in the smooth muscles of coronary arteries, an important decrease in coronary flow could occur. Indeed, since DCRP's first consult on these drugs in 2006, immunohistochemical staining has demonstrated that mu-, kappa-, and delta- opiod receptors are present in the human heart (Sabanski et al, Heart Vessels Jan 2014, DOI 10.1007/s00380-013-0456-5) (http://link.springer.com/article/10.1007%2Fs00380-013-0456-5). While

the authors hypothesize a role for these receptors in neural transmission and regulation of myocardial cell function, the clinical consequences of their activation and/or antagonism on the heart are unknown. It is interesting to note that one subject from the open-label MNTX study 3358 experienced the SAE of vasospastic angina. This subject was admitted to the hospital with chest pain and difficulty breathing and subsequently had ergonovine-induced coronary vasospasm in the catheterization laboratory involving the LAD and CFX coronary arteries that was reversed with 1000 mcg of IC nitroglycerin.

2. Drug induced electrical instability / repolarization abnormalities. No evidence of drug-induced proarrhythmic ECG changes has been demonstrated for any of these drugs.

3. Prothrombotic effects. These have not been demonstrated for any of these drugs, but for most if not all, this has not been systematically assessed.

For (b) (4) and Targiniq (oxycodone+naloxone), the sheer size of their development programs is reassuring, in that we would have expected to see the consequences of important drug-induced vasospasm or prothrombotic drug effects if these were occurring, and we did not. While the physiologic stress of withdrawal (be that central or peripheral) may not be well tolerated by patients with important underlying ischemic heart disease and/or stenotic valvular heart disease, the concomitant CV AEs that occurred in close proximity to non-CV AEs were for the most part non-serious, and none involved ischemic catastrophes. These two large databases argue against the presence of a class-effect CV safety risk for the opioid antagonists.

For Entereg, which is a distinctly different molecular structure than naloxone, study SB-767905/14 in non-cancer subjects with OBD randomized 538 to 0.5 mg Entereg twice daily and 267 to placebo. Seven MIs and three episodes of unstable angina were observed in subjects administered Entereg and none in subjects administered placebo. It is unclear whether this was a chance finding, or an outcome risk that is specific to this molecular entity (i.e., not a class effect). The sponsor chose not to complete a CV safety study, and the drug was placed under a REMs-ETASU.

For Relistor (methylnaltrexone), it is noted that:

- For this drug's approved indication (OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient), the label notes that the use of Relistor beyond four months was not studied.

- (b) (4) is likewise sparse, with only 4 weeks of controlled data in a small number of patients (b) (4)

- For some non-MACE CVAEs, there appeared to have been a temporal relationship between drug administration and the onset of symptoms, again, effecting a very small number of patients in a small overall safety dataset.

Relistor is chemically distinct from the other agents, and it is the only one of these four opioid receptor antagonists administered by subcutaneous injection. Whether the above findings are chance occurrences, drug-specific (i.e. non-class effect) occurrences that will have few if any major medical consequences long term, or drug-specific CV risk that is important but will occur with low frequency is uncertain due to the dearth of controlled safety data for this agent. Noted are the sponsor's arguments that CV AE rates were similar to historical controls of patients taking opioids. This argument would be more compelling if CV adverse outcomes had been predefined endpoints of study 3358, with the attendant stringency of CV event ascertainment that this would have involved, as well as a control group.

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/s/

PRESTON M DUNNMON
04/15/2014

NORMAN L STOCKBRIDGE
04/15/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 26, 2014
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 205777
Product Name and Strength:	Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) Extended Release Tablets 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Purdue Pharma L.P.
Submission Date:	February 14, 2014
OSE RCM #:	2013-2447
DMEPA Primary Reviewer:	Vicky Borders-Hemphill, PharmD
DMEPA Team Leader:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the proposed container labels, insert labeling, and Medication Guide for Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) Extended Release Tablets for risk of medication error in response to a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Container Labels

The Applicant proposes three strengths for this product supplied in 100-count bottles each. The three proposed container labels are differentiated by color which appears to be sufficient to mitigate product selection errors. However, as presented on the proposed labels, all three strength statements omit the unit of measure, milligram (mg), for the oxycodone hydrochloride component of the strength statement. The unit of measure is important information that must be displayed on the labels and omission may pose confusion as to the amount of ingredient per tablet. Additionally, we identified other areas that can be improved to reduce clutter and redundancy on the container labels, and we provide recommendations in section 4 below.

Insert Labeling and Medication Guide

The insert labeling and Medication Guide submitted September 23, 2013, referred to the proprietary name as Targiniq. The insert labeling and Medication Guide need to be revised to

incorporate the name Targiniq ER, granted on October 28, 2013, throughout. As with the container labels, strength statements throughout the insert labeling and Medication Guide omit the unit of measure, milligram (mg), for the oxycodone hydrochloride component of the strength statement and this needs to be revised to include this important information as stated above. Additional recommendations to improve readability of the insert labeling and include important information necessary for the safe use of this product are listed in Section 4.1.1. below.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container labels and labeling can be improved to mitigate the risk for medication errors. We request the recommendations in Section 4.1.2. be communicated to the Applicant prior to approval of the NDA.

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

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

4.1.1 Comments to the Division

A. Insert labeling and Medication Guide

1. Ensure that the proprietary name is revised from "Targiniq" to "Targiniq ER" throughout the insert labeling and Medication Guide.
2. Ensure that the unit of measure, milligram (mg), is added for the oxycodone hydrochloride component of the strength statement throughout the labeling since omission may lead to confusion regarding the amount of ingredient per tablet

B. Insert Labeling Highlights Section – Dosage and Administration

1. We recommend including the usual starting dose and the maximum daily dose in this section.

C. Full Prescribing Information – Section 2 (Dosage and Administration)

1. We recommend adding the statement "TARGINIQ ER is administered every 12 hours." to the first line in this section as it is important information that should be highlighted.

4.1.2 Comments to the Applicant

A. Container Labels

1. Ensure that the approved USAN established name is at least ½ the size of the proprietary name per *21 CFR 201.10(g)(2)*.
2. Add the unit of measure, milligram (mg), to the oxycodone hydrochloride component of the strength statement as this is important information

that must be displayed and omission may pose confusion as to the amount of ingredient per tablet.

3. Remove the (b) (4) from the principal display panel as it will reduce clutter and redundancy with information already contained on the side panel.
4. Relocate the Medication Guide statement to the lower third portion of the principal display panel (PDP) and remove the red-lined box from around the Medication Guide Statement so it does not compete with more important information on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Targiniq ER that Purdue Pharma L.P. submitted on September 23, 2013, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Targiniq ER and the Reference Listed Drugs [RLD]

Product Name	**Targiniq ER**	**Narcan** (RLD)	Oxycontin (RLD)
Active Ingredient	oxycodone HCl/naloxone HCl	naloxone HCl injection, USP	oxycodone HCl
Indication	For management of (b) (4)	For the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids	For the relief of moderate to severe pain where opioid analgesia is appropriate
Route of Administration	oral	Intravenous (IV), intramuscular (IM), or subcutaneous (SC)	oral
Dosage Form	Extended release tablet	Injection solution	Tablets
Strength	10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg	0.4 mg/mL, 1 mg/mL, 0.02 mg/mL	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dose and Frequency	One tablet every 12 hours up to a ceiling of 80 mg/40 mg/day	0.4 mg to 2 mg IV, IM, or SC, up to a total dose of 10 mg; doses may be repeated every 2 to 3 minutes, as needed	10 mg to 80 mg every 12 hours
How Supplied	100 tablets per bottle	10 Multiple dose vials per box and 110 preservative free ampules per box	100 tablets per bottle 10 tablets per unit dose blister card with two cards/ carton
Storage	25°C (77°F)	25°C (77°F)	25°C (77°F)
Container Closure	child-resistant closure, opaque plastic bottles	Vials and ampules	child-resistant closure, opaque plastic bottles and unit dose blisters

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Targiniq ER labels and labeling submitted by Purdue Pharma L.P..

- Container label submitted on February 14, 2014
- Insert Labeling submitted September 23, 2013
- Medication Guide submitted September 23, 2013

G.2 Label and Labeling Images

(b) (4)

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

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

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/s/

BRENDA V BORDERS-HEMPHILL
02/26/2014

IRENE Z CHAN
02/26/2014

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: APPLICATION NUMBER/SUPPLEMENT NUMBER

Application Type: New NDA/New BLA/Efficacy Supplement/PLR Conversion Supplement

Name of Drug: PROPRIETARY NAME (ESTABLISHED NAME/PROPER NAME) DOSAGE FORM

Applicant:

Submission Date:

Receipt Date:

1.0 Regulatory History and Applicant's Main Proposals

STATE WHAT THE APPLICATION PROVIDES FOR AND PROVIDE A VERY BRIEF REGULATORY HISTORY

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).

NOTE TO RPM: Additional PI review information including labeling guidances, the Labeling Review Tool as well as information about the OND PI review process can be found at:

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/UCM025576

3.0 Conclusions/Recommendations

CHOOSE A OR B

A. USE IF NO LABELING DEFICIENCIES WERE IDENTIFIED

No SRPI format deficiencies were identified in the review of this PI.

B. USE IF LABELING DEFICIENCIES WERE IDENTIFIED

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

IF APPLICABLE, LIST OTHER LABELING ISSUES

In addition, the following labeling issues were identified:

1.

RPM PLR Format Review of the Prescribing Information

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE (**CHOSE A DATE WITHIN TWO TO THREE WEEKS OF THE LETTER**). The resubmitted PI will be used for further labeling review.

INSTRUCTIONS FOR COPYING ITEMS FROM SRPI TO 74-DAY OR ADVICE LETTER:

The SRPI is "protected" (or "locked") to allow use of the drop-down menus. However, the "protection" mode does not allow you to directly copy the SRPI item into the 74-day or advice letter.

To copy SRPI items in the letter, after completion of the 48-item SRPI checklist, unprotect (or unlock) the document:

Microsoft Word 2003
(1) Click on the "Tools" tab, then (2) click on "Unprotect Document."

Microsoft Word 2007
(1) Click the "Review" tab, (2) click on "Protect Document", (3) on "Restrict Formatting and Editing" window click "Stop Protection" at the bottom of the window, and (3) click "OK" (leave the password box blank).

If you need to switch from the "unprotected" mode back to the "protected" mode to allow use of the drop-down menus:

Microsoft Word 2003
(1) Click the "Tools" tab (2) click on "Protect Document", (3) click on "Yes, Start Enforcing Protection" in the right-sided task pane, and (4) click "OK" (leave the password box blank).

Microsoft Word 2007
(1) Click the "Review" tab, (2) click on "Protect Document" tab, (3) click on "Restrict Formatting and Editing", (4) click on "Yes, Start Enforcing Protection", and (5) click "OK" (leave the password box blank).

[END INSTRUCTION: DELETE ALL INSTRUCTIONS BEFORE DARRTS CHECK-IN.]

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.

INSTRUCTIONS FOR COMPLETING THE SRPI
There is one drop-down menu and one comment field for each item.

Drop-Down Menu: "NO" is the default option. For each SRPI item, click on the word "NO" and choose one of three following options:

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

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word "*Comment*" and insert your comment.

[END INSTRUCTION: DELETE ALL INSTRUCTIONS BEFORE DARRTS CHECK-IN.]

Highlights (HL)

GENERAL FORMAT

NO 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:

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 is 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:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

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

Comment:

NO 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:

NO 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:

NO 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

NO 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

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:

Product Title

NO 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 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:

Boxed Warning

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

Comment:

NO 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:

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" centered immediately beneath the heading.

Comment:

NO 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:

NO 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

NO 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

NO 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

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".

Comment:

NO 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).

Comment:

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:

Dosage Forms and Strengths

NO 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:

Contraindications

NO 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:

NO 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 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:

Patient Counseling Information Statement

NO 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:

Revision Date

NO 27. **Bolded** revision date (i.e., **"Revised: MM/YYYY** or **Month Year"**) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment:

NO 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 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:

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:

NO 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

NO 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 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:

Full Prescribing Information (FPI)

GENERAL FORMAT

NO 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **"FULL PRESCRIBING INFORMATION".**

Comment:

NO 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO

Selected Requirements of Prescribing Information (SRPI)

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
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:

NO 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:

NO 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:

NO 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.

Comment:

Selected Requirements of Prescribing Information (SRPI)

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

NO 42. All text is **bolded**.

Comment:

NO 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:

NO 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:

Contraindications

NO 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 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:

NO 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:

Patient Counseling Information

NO 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:

CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 205777
NDA Type: Standard Review, Abuse Deterrent 505 (b) (2)

Applicant: Purdue Pharma

Stamp Date: September 23, 2013 (Electronic Submission)
PDUFA Date: 7/23/14
Advisory Committee: Yes. No date set yet

Drug Name: Oxycodone Hydrochloride/Naloxone Hydrochloride

IND Number: 70851

On initial overview of the NDA/BLA application for filing:

	Checklist	Yes	No	NA	Comment
	What is the regulatory history of this application?	x			Prior CSS' reviews, DARRTS, IND 70851, Love Lori A, dated 5/23/13, 8/15/12, 1/30/12, 8/05/11
	Abuse potential assessment is required if any of the following are true for a drug:[1,2]				
	It affects the CNS	x			
	It is chemically or pharmacologically similar to other drugs with known abuse potential	x			
	It produces psychoactive effects such as sedation, euphoria, and mood changes	x			
	Content of NDA abuse potential section:				
	Module 1: Administrative Information and Prescribing Information 1.11.4 Multiple Module Information Amendment contains:				
	• A summary, interpretation, and discussion of abuse potential data provided in the NDA.	x			
	• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.	x			
	• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA	x			Oxycodone containing products are in Schedule II of the CSA. The Sponsor is not pursuing scheduling changes
	Module 2: Summaries 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.				
		x			
	Module 3: Quality				
	3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).	x			
	Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?	x			
	3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.	x			
	Is the drug a new molecular entity?		x		

[1] 21 CFR 314.50(d)(5)(vii): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

[2] 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

CSS Filing Checklist for NDA/BLA or Supplement

	Checklist	Yes	No	NA	Comment
	Is this a new or novel drug formulation?	x			
	Is this an extended release formulation?	x			Proposed strengths (b) (4) 10/5 mg, 20/10 mg and 40/20 mg oxycodone/naloxone
	Is this an abuse-resistant formulation?	x			This is an extended release, claimed to be abuse deterrent formulation. The Sponsor claims that the presence of naloxone will deter oral chewing, intravenous and intranasal abuse
	Module 4: Nonclinical Study Reports				
	4.2.1 Pharmacology	x			
	4.2.1.1 Primary Pharmacodynamics - contains study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.	x			
	Are in vitro receptor binding studies included?	x			Literature Cited
	Are functional assays included?	x			
	4.2.3.7.4 Dependence – section includes:				
	• A complete discussion of the nonclinical data related to abuse potential. • Complete study reports of all nonclinical abuse potential studies.				
	Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA				
	Was a self administration study conducted?		x		Literature Cited Only
	Was a conditioned place preference study conducted?		x		
	Was a drug discrimination study conducted?		x		Literature Cited Only
	Was a physical dependence study conducted?	x			Animal study has been conducted
	Module 5: Clinical Study Reports 5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.				
	Human abuse potential study:				
	Was a human abuse potential study conducted?	x			Four human abuse potential studies were conducted Two studies were conducted in a non-dependent recreational drug user population, to evaluate the safety and PK profile of the formulation when taken orally, IV or IN (Study ONU1003), and to evaluate the safety and PK profile of the chewed and intact formulation (Study ONU 1007) Two additional studies were conducted in a methadone maintained opioid dependent population to evaluate the PK/PD (including withdrawal), and safety of chewed formulation compared to Oxy API (Study ONU1004), and PK/PD (including withdrawal) and safety of the intact and chewed formulation relative to Oxy API (Study ONU1008)
	Are all the primary data included in the NDA?	x			
	Is a Statistics consult necessary?	x			Office of Biostatistics has been involved during IND, and CSS has already placed a consult for the review of the four abuse

CSS Filing Checklist for NDA/BLA or Supplement

	Checklist	Yes	No	NA	Comment
					potential studies provided under this NDA (See DARRTS, NDA 205777, Saltz, Sandra L., 10/ 22/13 General Consult Request)
	Other Clinical trials:				
	Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]?	x			Case Report Forms for Adverse Events related to abuse potential, compliance and diversion, and overdose associated with misuse and abuse are provided
	5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product				
	Postmarketing experience				15-day Safety Reports have been submitted to IND 70851
	Did you review the scientific literature?	x			
	Did you conducted a search of databases and other information related to misuse, abuse, and addiction?	x			
	Is there evidence for any of the following:				
	Accidental overdose in the patient population and vulnerable populations			x	Review issue
	Overdose associated with misuse and abuse	x			Overdose data are provided
	Unintended pediatric exposures to product		x		
	Labeling issues				
					Proposed label is provided
	Drug disposal issues?		x		Review issue
	Postmarketing activities [PMRs, PMCs, REMS]	x			
	Scheduling activities			x	

Is NDA FILEABLE from a CSS perspective? _____Yes_____

If the Application is not fileable, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CSS does not have any review issues regarding NDA 205777

CSS Reviewer: James M. Tolliver, Ph.D., Pharmacologist Date: 11-27-2013

Team Leader: Silvia N. Calderon, Ph.D., Interdisciplinary Date: 12-3-2013

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

/s/

SILVIA N CALDERON
12/03/2013

MICHAEL KLEIN
12/03/2013