CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208271Orig1s000

OTHER REVIEW(S)

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 # 208271
Product Name: RELISTOR

PMR/PMC Description: A post-marketing, observational epidemiologic study comparing oral Relistor (methylnaltrexone bromide) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to oral Relistor (methylnaltrexone bromide)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among oral Relistor (methylnaltrexone bromide) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the oral Relistor (methylnaltrexone bromide)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of oral Relistor (methylnaltrexone bromide) exposure at the end of the study.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	07/01/2017
	Study/Trial Completion:	04/01/2024
	Final Report Submission:	07/01/2025
	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 adult studies are completed and ready for approval. The risk for MACE stems from another drug in the PAMORA class (alvimopan) and is theoretical for Relistor.

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 PAMORA class includes alvimopan (Entereg®, NDA 021775), naloxegol (Movantik®, NDA 204760), and methylnaltrexone bromide (Reslitor®, NDA 021964 and NDA 208271). An unresolved safety concern derives from GSK014, a 12-month double blind and placebo-controlled randomized safety study of alvimopan, 0.5 mg twice daily, for opioid bowel dysfunction in chronic non-cancer pain. GSK014 identified 14 (2.6%) alvimopan and 0 (0.0%) placebo patients with cardiovascular events. These results from Entereg® GSK014 triggered substantial regulatory concern in FDA about the cardiovascular safety of all PAMORA drugs. The clinical information submitted subsequently with new drug applications for Movantik® and Relistor® proved insufficient to dispel FDA concerns.

In particular, NDA 021964 and NDA 208271 for SQ and oral Relistor® lacked controlled clinical information about long-term safety. DEPI-I believes that the theoretical cardiovascular risk for Relistor, given that it is in the same class as Entereg (alvimopan) which has a potential signal for cardiovascular risk, is adequate to indicate an unexpected serious risk related to Relistor use.

To identify an unexpected serious risk of major adverse cardiac events (MACE) defined as acute myocardial infarction (AMI), stroke, and cardiovascular death in the postmarketing setting, protocol-based, well-controlled, and adequately powered studies are necessary to test specific research hypotheses.

DEPI-I has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) or the new pharmacovigilance system Active Risk Identification and Analysis (ARIA) established under subsection 505(k)(3) of the FDCA will not be sufficient to identify the unexpected serious risks of MACE related to the use of Relistor. DEPI-I therefore requests a required post-marketing safety study (PMR) under section 901 of FDAAA 2007 Title IX to identify an unexpected serious risk when available data indicates the potential for a serious risk related to the use of Relistor.

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 post-marketing, observational epidemiologic study comparing Relistor (methylnaltrexone bromide) to other treatments of opioid induced constipation in patients with chronic non-cancer pain.

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.*

_____

(signature line for BLAs)

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 22, 2016
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	RELISTOR (methylnaltrexone bromide)
Dosage Form and Route:	tablets, for oral use injection, for subcutaneous use
Application Type/Number:	NDA 208271
Applicant:	Salix Pharmaceuticals, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc., with its affiliate, Valeant Pharmaceutical North America being the communicant

1 INTRODUCTION

On June 19, 2015, Salix Pharmaceuticals, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc., with its affiliate, Valeant Pharmaceutical North America being the communicant, submitted for the Agency's review 505(b)(1) New Drug Application (NDA) 208271 for RELISTOR (methylnaltrexone bromide) tablets. The proposed indication for RELISTOR tablets is for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. The Applicant cross-references all data contained in RELISTOR Subcutaneous Injection NDA 021964/S-010 approved for the treatment of OIC in adult patients with chronic non-cancer pain on September 29, 2014. RELISTOR (methylnaltrexone bromide) Subcutaneous Injection NDA 021964 was originally approved on April 24, 2008, for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

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 Gastroenterology and Inborn Errors Products (DGIEP) on June 22, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for RELISTOR (methylnaltrexone bromide) tablets and RELISTOR (methylnaltrexone bromide) injection.

2 MATERIAL REVIEWED

- Draft RELISTOR (methylnaltrexone bromide) tablets MG and IFU received on June 19, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2016.
- Draft RELISTOR (methylnaltrexone bromide) tablets Prescribing Information (PI) received on June 19, 2015, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on June 14, 2016.
- Approved RELISTOR (methylnaltrexone bromide) Subcutaneous Injection comparator labeling dated September 29,2014.

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.

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. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are 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 and IFUs are 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 or IFUs.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
06/22/2016

MEETA N PATEL
06/22/2016

LASHAWN M GRIFFITHS
06/22/2016

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: June 21, 2016

To: Lawrence Allan
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208271
OPDP Comments for proposed draft PI, MG, and IFU for RELISTOR® (methylnaltrexone bromide) tablets, for oral use and
RELISTOR® (methylnaltrexone bromide) injection, for subcutaneous use

OPDP has reviewed the proposed draft PI Relistor. We have no additional comments.

Comments on the proposed patient labeling will be submitted under a separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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

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/s/

MEETA N PATEL
06/21/2016

DATE: June 9, 2016

FROM: Robert Ball, MD, MPH, ScM,
Deputy Director, Office of Surveillance and Epidemiology, CDER, FDA

SUBJECT: Oral Relistor ARIA Sufficiency Memo

I concur with the lack of sufficiency of ARIA for evaluating this oral Relistor safety issue and make the following observations.

1) The standards against which ARIA sufficiency are being compared are those for Safety Outcome Trials and the FDA Best Practice Guidance for Conducting and Reporting Pharmacoepidemiology Safety Studies Using Electronic Healthcare Data. These are very high standards but the decision to use those standards is the key to this determination.
2) The justification for using these standards in this particular situation is well described in the memo, but is relatively unique to this situation's scientific and regulatory history and may not apply in future situations.
3) In several of the findings of lack of sufficiency (e.g. missing information on out of hospital deaths and behavioral and preventive practices of study patients), the lack of information *in itself* is considered grounds for lack of sufficiency. A more nuanced approach would involve assessing the quantitative impact of the lack of information, and the potential for biased findings, relative to the effect size of interest and should be considered for future sufficiency determinations.
4) The lack of sophisticated diagnostics for assessing statistical model appropriateness is cited as a reason for lack of sufficiency. This might be the most easily solved of the cited issues and whether it can be remedied in the ARIA tools is worth exploring.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo
Version: 2016-02-11

Date:	June 9, 2016
Reviewer(s):	Joel L. Weissfeld, MD MPH, Medical Officer Division of Epidemiology I
Team Leader:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Deputy Division Director:	David Shih, MD MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name(s):	methylnaltrexone bromide tablet (Relistor®)
Application Type/Number:	NDA 208271 (IND 067452)
Applicant/sponsor:	Salix Pharmaceuticals
OSE RCM #:	RCM Number: 2015-1410

As secondary and tertiary reviewers, we arrive at the same conclusion as the primary reviewer, who explains his opinion in the following pages. Our rationale differs slightly, however.

We conclude ARIA lacks sufficiency to answer the present regulatory question, quantifying the association between methylnaltrexone use and subsequent MACE (major adverse cardiovascular event) on the grounds that ARIA lacks the ability to:

1. Adequately ascertain unhospitalized cardiovascular death, an important component of MACE.
2. Ascertain important cardiovascular risk factors (such as smoking and over-the-counter aspirin use) – carrying the potential to confound the association.

The primary reviewer agrees with the above limitations. However, unlike the primary reviewer, we believe ARIA might have sufficient capacity to ascertain the study population and exposure status reasonably well. We believe:

- The presence of multiple prescriptions for opioids and constipation therapies is a reasonable method to identify the study population of interest – patients with chronic pain and opioid-induced constipation. Validation methods attempts might lead to ascertainment that is no more valid than claims data alone. For instance, to ensure multiple opioid prescriptions are not due to drug diversion, chart validation or patient interview would probably lead to the same findings, as patients are not likely to admit drug diversion, in interviews with researchers or the prescribers.
- Pharmacy claims data adequately ascertain prescription drug exposure. There is a preponderance of scientific precedence of pharmacoepidiomologic studies using claims data for this purpose. Furthermore, attempts at validating pharmacy claims might lead to less valid findings. Although chart validation might identify prescriptions written for patients, prescriptions are less reliable an indicator of patient use than claims. The mere presence of a medical record prescription fails to support whether the patient even picked-up the medication from the pharmacy. Self-report also has limitations, as patients might fail to recall medications taken and/or the days in which they took the medication.

Regardless of the differences in opinion of ARIA sufficiency for the above two elements, study population and exposure status ascertainment, we all have consensus that ARIA fails sufficiency in ascertaining at least two important elements: 1) unhospitalized cardiovascular death and 2) important cardiovascular risk factors. Therefore, we all arrive at the same conclusion that overall, ARIA lacks sufficiency in the present situation.

We intend for this determination (and its rationale) to lack impact on future sufficiency determinations. That is, we are not setting any precedent for future investigations of drug safety issues because each drug-adverse event pairing has unique considerations, and the need for different levels of evidence.

Sukhminder K. Sandhu, PhD, MPH, MS
Secondary Reviewer
DEPI I Team Leader

David Shih, MD, MS
Tertiary Reviewer
DEPI I Deputy Director

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	X
-Interim	
-Final	
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

1. BACKGROUND INFORMATION

1.1. Medical Product

For methylnaltrexone bromide oral tablet, Relistor® NDA 208271 seeks FDA approval for the indication, opioid-induced constipation in adults with chronic non-cancer pain.

Methylnaltrexone bromide belongs to a class of drugs known as peripherally acting mu-opioid receptor antagonists (PAMORA). PAMORAs aim to restore normal bowel motility in constipated opioid-treated patients by blocking opioid interactions with intestinal mu-opioid receptors.

During review and approval of methylnaltrexone bromide subcutaneous (SQ) injection (Relistor® NDA 021964), FDA could not identify "a definitive pathophysiological basis" for cardiovascular disease risk from mu-opioid receptor antagonists.[1]

1.2. Describe the Safety Concern

The PAMORA class includes alvimopan (Entereg®, NDA 021775), naloxegol (Movantik®, NDA 204760), and methylnaltrexone bromide (Relistor®, NDA 021964 and NDA 208271). An unresolved safety concern derives from GSK014, a 12-month double blind and placebo-controlled randomized safety study of alvimopan, 0.5 mg twice daily, for opioid bowel dysfunction in chronic non-cancer pain. GSK014 randomized 538 patients to alvimopan, 0.5 mg twice daily, and 267 patients to placebo. With 173 of 538 (32%) alvimopan and 74 of 267 (28%) placebo patients followed on treatment for 360 days, retrospective analysis of GSK014 identified 14 (2.6%) alvimopan and 0 (0.0%) placebo patients with cardiovascular events.[2] The 14 alvimopan patients with cardiovascular events included 11 (1 fatal) with ischemic events (myocardial infarction, unstable angina, or cerebrovascular accident) and 3 with other serious cardiovascular events (congestive heart failure or serious arrhythmia). When analyzed "according to [a] strict [major adverse cardiovascular event] MACE definition" developed for purposes of a June 2014 Anesthetic and Analgesic Drug Products Advisory (AADPAC) Committee Meeting, FDA reported one alvimopan-treated patient with cardiovascular death and six alvimopan-treated patients with non-fatal myocardial infarction (CDER, 2014, Page 17[2]). Seven, five, and two alvimopan-treated patients in GSK014 suffered a cardiovascular event 31-90, 91-180, and >180 days after randomization (Memorandum of Statistical Consultation, 2008[2]).

These results from Entereg® GSK014 triggered substantial regulatory concern in FDA about the cardiovascular safety of all PAMORA drugs. Although sufficient for NDA approval, the clinical information submitted subsequently with new drug applications for Movantik® and Relistor® prompted FDA to call for further investigation of this theoretical class-wide safety issue concerns.

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[1] Center for Drug Evaluation and Research, September 29, 2014, Division Director Summary Review for NDA 021964/S010, Page 12.

[2] Adolor Corporation, August 9, 2008, Alvimopan Safety Update, Retrieved from \\fdswa150\NONECTD\N21775\N_000\2007-08-09\update on February 19, 2016.

Memorandum of Statistical Consultation, NDA 021775 (alvimopan), signed 4/16/2008.

Center for Drug Evaluation and Research (CDER), January 30, 2014, Briefing Document for June 11-12, 2014, Anesthetic and Analgesic Drug Products Advisory Committee Meeting, Retrieved from http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm on February 19, 2016, Page 17.

In particular, NDA 021964 and NDA 208271 for SQ and oral Relistor® lacked controlled clinical information about long-term safety, in the context of concerning safety data in a drug of the same class. In place of pre-approval controlled clinical information, the AADPAC "stated that post-marketing observational studies may also be conducted (post-approval)."[3]

Concerned about risk-benefit balance, FDA questioned the approvability of PAMORA drugs for non-life threatening indications, such as, constipation from chronic opioid use. To secure favorable risk-benefit balance, FDA (b) (4) approved a post-operative ileus indication for Entereg®, with use restricted by a Risk Evaluation and Mitigation Strategy (REMS). In addition, acting on advice delivered by the AADPAC in June 2014, FDA approved Movantik® (NDA 204760) and Relistor® subcutaneous injection (NDA 021964) for opioid-induced constipation, but required post-market studies to verify cardiovascular safety.

The September 2014 approval letters for Movantik® and Relistor® subcutaneous (SQ) injection included identical language for post-market required (PMR) studies 2779-1 and 2787-1, respectively. Specifically, these PMRs required observational epidemiologic studies of major adverse cardiovascular event (MACE) risk from PAMORAs when used to treat opioid-induced constipation. PMR studies 2779-1 and 2787-1 specified standards appropriate to protocol-based, well-controlled, and adequately powered studies designed to test specific research hypotheses. These standards included,

1. Pre-specified primary and secondary hypotheses.
2. Means to ascertain and validate MACE, defined as a composite of myocardial infarction, stroke, or cardiovascular death.
3. Special protections against biases sometimes created by selecting prevalent users for study.
4. Appropriately conceived comparator populations (control groups).
5. Consideration of important potential confounding variables that included cardiovascular lifestyle risk factors and cardio-protective over-the-counter medications (e.g., low-dose aspirin).
6. Special efforts to identify patients treated continuously long-term (at least 12-months) with the PAMORA drug of concern.

In epidemiology, these features describe the observational study analog of a randomized clinical trial (RCT) for long-term cardiovascular safety.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[3] Center for Drug Evaluation and Research, June 11-12, 2014, Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting, Retrieved from http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm on March 2, 2016.

1.4. Statement of Purpose

To identify an unexpected serious risk when available data indicate potential for serious risk, FDA identifies a need for post-market study of the long-term cardiovascular safety of oral Relistor® when used to treat opioid-induced constipation. Noting a delicate risk-benefit balance, FDA judges as insufficient the controlled long-term clinical safety data from PAMORA pre-market programs. Consistent with this judgment, FDA conditioned approval of Movantik® NDA 204760 and SQ Relistor® NDA 021964 on PMR studies 2779-1 and 2787-1. In discussions with industry, FDA requested post-market studies designed to (1) test a specific safety hypothesis centered on MACE, (2) estimate risks precisely, and (3) enable secure conclusions about cause and effect.

(b) (4)

Section 2 (below) grades the FDA-supported Active Risk and Identification Analysis (ARIA) System, as currently implemented in Sentinel. Guided by the Statement of Purpose in the previous paragraph, Section 2 determines if ARIA lacks sufficient capabilities to investigate this safety issue, thereby requiring a protocol-based assessment, in electronic healthcare data, of MACE risk, as extended to oral Relistor® (NDA 208271). As the standard for analysis, DEPI uses FDA guidance for Best Practices for Conducting and Reporting Pharmacoepidemiology Safety Studies Using Electronic Healthcare Data.[5] See Section 7 (below) for a discussion of the possible policy implication of this standard for judging ARIA sufficiency.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Because of the nonfatal nature of the medical indication for use (constipation) and the seriousness of the safety signal, FDA requires post-market studies designed to exclude a moderate 2-fold excess MACE risk from oral Relistor®.

1.6. Other Information Relevant to FDA Decision Making

The Risk Management Plan submitted with NDA 208271 referred to,

1. MACE as a "potential risk identified by FDA as 'new safety information'".
2. (b) (4) post-marketing requirement (PMR) for an observational epidemiologic study comparing SC RELISTOR to other treatments of OIC [opioid-induced constipation] in patients with chronic non-cancer pain."
3. Plans for ongoing monitoring of clinical trials and post-marketing reports to "include a targeted review for cardiovascular events observed in the setting of Relistor treatment at the active moiety level as well as by specific formulation (i.e., oral and subcutaneous Relistor treatment)."

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[4] (b) (4)

[5] Center for Drug Evaluation and Research, May 2013, Best Practices for Conducting and Reporting Pharmaco-epidemiology Safety Studies Using Electronic Healthcare Data, Retrieved from http://www.fda.gov/RegulatoryInformation/Guidances/ on March 7, 2016.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The source population consists of adults (≥18 years of age). Study selection from the source population requires evidence for (1) opioids used for chronic non-cancer pain and (2) constipation caused by opioids.

2.2 Is ARIA sufficient to assess the intended population?

ARIA permits identification of cancer-diagnosis-free patients, dispensed prescriptions for opioid medications. However, ARIA lacks validated methods for identifying patients with chronic pain or constipation caused by opioids. Identification of the intended population in ARIA requires strong assumptions, which accept (1) multiple opioid prescriptions as an indicator for chronic pain and (2) concomitant prescriptions for opioids and constipation treatments as an indicator for opioid-induced constipation. Therefore, ARIA is not sufficient to assess the intended population. Sufficiency in this domain may require medical record review studies to validate prescription claims, for opioid and constipation treatments, as indicators of constipation caused by opioids in patients with non-cancer pain.

2.3 Commentary

The Best Practices Guidance regards selection of an appropriate control group as "a *critical part* [*emphasis added*] of a pharmacoepidemiologic safety study" (Page 14[5]). For cohort studies, specifically, the Guidance identifies, as the ideal, designs with a "comparator group taking a drug used to treat the same disease, with the same level of disease severity, and from the same time period as the exposed cohort." Tian, et al., 2013,[6] suggest that satisfactory identification, in retrospectively collected data, of chronic pain (one component defining the PAMORA-intended population) may require medical record information typically excluded from administrative data. Also, DEPI is aware of only limited evidence for the validity of code-based algorithms for identifying patients with constipation.[7] For drugs used to treat opioid-induced constipation in chronic non-cancer pain, post-market safety studies could use prospective study methods to satisfy this Guidance standard related to identification of the intended population. Alternatively, as noted above, post-market safety studies in administrative data could possibly satisfy this standard through parallel studies of the validity of code-based algorithms used to select study populations.

3 EXPOSURES

3.1 Treatment Exposure(s)

DEPI defines the treatment exposure as time at risk following the new use of methylnaltrexone bromide oral tablet.

3.2 Comparator Exposure(s)

DEPI attaches value to study designs with two comparator exposures. Therefore, DEPI defines a PAMORA comparator exposure as time at risk following the new use of naloxegol (Movantik®).

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[6] Tian, TY, I Zlateva and DR Anderson, 2013, Using Electronic Health Records Data to Identify Patients with Chronic Pain in a Primary Care Setting, J Am Med Inform. Assoc, 20:e275-e280.

[7] Sands, BE, MS Duh, C Cali, A Ajene, RL Bohn, D Miller, JA Cole, SF Cook and AM Walker, 2006, Algorithms to Identify Colonic Ischemia, Complications of Constipation and Irritable Bowel Syndrome in Medical Claims Data: Development and Validation, Pharmacoepidemiol Drug Saf, 15:47-56.

DEPI defines a non-PAMORA comparator exposure as time at risk following the new use of lubiprostone (Amitiza®) or linaclotide (Linzess®), two prescription medications indicated for opioid-induced and chronic idiopathic constipation, respectively.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA permits identification of patients dispensed outpatient prescriptions. However, ARIA lacks methods for verifying patient adherence. Therefore, identification of treatment and comparator exposures in ARIA requires a strong assumption, which accepts dispensed prescriptions as an indicator for adherent use. Lacking procedures to validate dispensed prescriptions as an indicator for adherent use, ARIA is not sufficient to identify the exposures of interest. Sufficiency in this domain may require either prospective collection of information about medication adherence (e.g., pill counts) or possibly medical record review studies to validate prescriptions claims as indicators for adherent medication use.

3.4 Commentary

The Best Practices Guidance observes that electronic healthcare data "do not capture patients' actual drug exposure because this depends on patients' adherence to the prescribed therapy" (Page 19[5]). To conform to customary practice in pharmacoepidemiology, DEPI usually accepts, out of practical necessity, the uncertainty inherently caused by trust in prescription claims as proxies for the exposures of interest. However, constipation symptoms commonly vary in severity over time and often respond to medical treatments prescribed for use as needed. When combined with a purpose statement that calls for the observational study analog of a long-term cardiovascular safety RCT, these clinical features of constipation may introduce unacceptable uncertainty into observational studies that rely solely on prescription claims. To allay this uncertainty, post-market PAMORA safety studies may require prospective study methods with patient adherence monitored in real time or retrospective studies in administrative data with parallel studies of the validity of prescription claims as proxies for the exposures of interest.

4 OUTCOME(S)

4.1 Outcomes of Interest

To assess ARIA sufficiency, DEPI accepts, as the outcome of interest, major adverse cardiovascular events (MACE), an FDA-standard clinical trial composite, defined by the incident occurrence of myocardial infarction, stroke, or cardiovascular death.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA permits adequate identification of fatal or non-fatal myocardial infarction and stroke, if occurrence results in admission to hospital. However, ARIA is currently unable to ascertain immediately fatal out-of-hospital myocardial infarction or stroke. Moreover, ARIA lacks validated methods for identifying (1) sudden cardiac death from severe ventricular arrhythmia and (2) cardiovascular deaths from causes other than myocardial infarction, stroke, or severe ventricular arrhythmia. MACE studies suited for hypothesis-driven analysis require methods that ascertain and characterize out-of-hospital deaths. Because the Statement of Purpose specifies a regulatory need to test hypotheses about a MACE outcome, ARIA is not sufficient to assess the outcome of interest. Sufficiency in this domain may require (1) active patient follow-up or data linkages to population-based death registries and (2) possibly access to paper or electronic medical records for blinded and independent outcome validation.

4.3 Commentary

The Best Practices Guidance observes, "Death is a particularly difficult outcome to ascertain reliably and completely using electronic healthcare data" (Page 21[5]). Moreover, the Guidance states that "reliable ascertainment of deaths can *only* [*emphasis added*] be accomplished through linkage with vital statistics or other systems" (Page 21[5]), capabilities currently lacking in ARIA.

5 COVARIATES

5.1 Covariates of Interest

Well-controlled studies that use observational (non-randomized) data require understanding about covariates (confounding variables) plausibly associated with both the exposures of interest and outcome of concern. For sake of discussion, DEPI identifies 36 potentially important covariates, in eight categories, with information possibly available in ARIA, including,

1. Three demographic covariates for (a) sex, (b) calendar year of cohort entry, and (c) age at cohort entry.

2. Five chronic pain covariates[8] for (a) pain (ICD-9 338, 339)[9], (b) disorders of the peripheral nervous system (ICD-9 350-357), (c) headache syndromes (ICD-9 339, 346), (d) arthropathies (ICD-9 710-719), and (e) dorsopathies (ICD-9 720-724).

3. Two covariates[8] to represent medical indications for methylnaltrexone or comparator treatment, including (a) constipation (ICD-9 564.0) and (b) irritable bowel syndrome (ICD-9 564.1).

4. Two covariates[8] to represent cardiovascular disease risk, including (a) essential hypertension ICD-9 401) and (b) diabetes without mention of complication (ICD-9 250.0).

5. Five covariates[8] to represent coexisting comorbidity, including (a) ischemic heart disease (ICD-9 410-414), (b) diseases of the circulatory system, except ischemic heart disease and essential hypertension (ICD-9 390-459, except 410-414 and 401), (c) diseases of the digestive system except constipation and irritable bowel syndrome (ICD-520-579, except 564.0 and 564.1), (d) mental disorders (ICD-9 290-319), and (e) diabetes with mention of complication (ICD-9 250.1-250.9).

6. Twelve covariates[10] to represent recent or concomitant treatments with (a) drugs for acid-related disorders (ATC A02)[11], (b) drugs for functional gastrointestinal disorders (ATC A03), (c) drugs for constipation (ATC A06), (d) drugs used in diabetes (ATC A10), (e) antithrombotic agents

[8] Covariate defined by a diagnostic code from specified code groupings found in any inpatient or outpatient claim for medical encounters in the 183 days before a first prescription claim for methylnaltrexone bromide oral tablet or comparator.

[9] Tentative ICD-9 codes shown for reference purposes, with ICD-10 translation anticipated for implementation in Sentinel.

[10] Covariate defined by any prescription claim in the 183 days before a first prescription claim for methylnaltrexone bromide oral tablet or comparator.

[11] WHO Anatomical Therapeutic Chemical (ATC) class, 2nd level.

(ATC B01), (f) cardiac therapies (ATC C01), (g) anti-hypertensive drugs (ATC C02), (h) diuretics (ATC C03), (i) beta blocking agents (ATC C08), (j) agents acting on the renin-angiotensin system (ATC C09), (k) lipid modifying agents (ATC C10), and (l) anti-inflammatory and anti-rheumatic products (ATC M01)

7. Three covariates to represent medical care use, in the 183 days before a first prescription claim for methylnaltrexone bromide oral tablet or comparator, including (a) number of hospitalizations, (b) number of outpatient physician visits, and (c) number of prescriptions.

8. Four covariates related to behavioral and preventive practices, including (a) smoking, (b) obesity, (c) physical inactivity, and (d) non-use of over-the-counter low-dose aspirin.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA permits adequate measurement for covariates in seven of eight categories listed above. However, ARIA currently lacks credible methods for measuring covariates in the eighth category, behavioral and preventive practices. Lacking information about the behavioral and preventive practices of study patients, ARIA is not sufficient to assess all covariates of interest. Sufficiency in this domain may require prospective data collection (e.g., direct patient questionnaire) or access to medical records, in paper or electronic formats, to measure differences between exposure groups according to the frequency of important behavioral and preventive practices.

5.3 Commentary

The Best Practices Guidance observes, "Unmeasured confounders can affect the study validity" (Page 16[5]). Assessing the potential for unmeasured confounding requires judgments, informed by (1) study-population-specific knowledge about the associations between unmeasured confounders and the disease outcomes of interest, (2) study-population-specific knowledge about the differences between exposure groups with respect to the unmeasured confounders, and (3) study-setting appreciation of the strengths or weaknesses of the indirect methods available for confounder control (e.g., propensity score methods for exposure matching or statistical adjustment). For studies primarily completed in electronic healthcare data, the Guidance specifically mentions "supplemental information" obtained by survey or medical record review as one way "to explore the potential impact of unmeasured confounders" (Page 16[5]).

As noted above, under Section 1.2, in regards to PAMORA PMR studies 2779-1 and 2787-1, earlier FDA decision making established, as a matter of critical concern, potential confounding through cardiovascular lifestyle risk factors and cardio-protective over-the-counter medications. This ARIA sufficiency analysis for oral Relistor® accepts, without critical reappraisal, precedents set by these earlier FDA decisions.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The Statement of Purpose requires inferential analysis, with confounder control, for MACE risk after exposure to oral Relistor®.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA currently includes stock tools for inferential analysis, including Cox proportional hazards regression with confounder control achieved by means of propensity score matching or stratification. However, hypotheses-driven protocol-based observational research typically requires flexible programming to assess, at a minimum, adequacy of confounder control and sensitivity of results to study assumptions. Because of this requirement for flexible programming, ARIA is not sufficient with respect to analytic tools available to assess the question of interest.

6.3 Commentary

The Best Practices Guidance observes, "Diagnostics, both graphical and analytical, are often relevant and facilitate the evaluation of assumptions and performance of the techniques" used "to address confounding and effect modification" (Page 23[5]). The distributed common data model used by Sentinel inhibits flexible diagnostic analysis. Routine diagnostics available in ARIA may suffice for safety surveillance, but not for protocol-based research using observational study methods.

7 NEXT STEPS

As noted in Section 1.4 (above), FDA has unique concerns about the cardiovascular safety of PAMORA drugs when used to treat opioid-induced constipation. Because of these concerns, as reflected in previous pre-ARIA FDA actions related to Movantik® NDA 204760 and SQ Relistor® NDA 021964, DEPI used a high standard in Sections 2-7 to judge capabilities in ARIA in relation to oral Relistor® NDA 208271. Specifically, DEPI used a standard appropriate to protocol-based observational studies designed to test one or more research hypotheses specific to a distinct safety concern. This high standard might not apply to indistinct safety concerns more conducive to active adverse event surveillance in ARIA.

DEPI recognizes that application of a lower standard might reach different conclusions about the appropriateness of ARIA as a regulatory means to help characterize a PAMORA safety concern. In this context, for example, judgments of ARIA sufficiency might regard hospitalization for acute myocardial infarction or stroke as acceptable proxies for a more generalized concern about cardiovascular safety. For purposes of active surveillance of adverse cardiovascular events associated with PAMORA use, judgments of ARIA sufficiency might accept preliminary results rendered less certain because of missing information about lifestyle factors related to cardiovascular disease risk. Simply, with two arguably appropriate analytic standards, a higher standard for protocol-based research and lower standard for active adverse event surveillance, DEPI could easily reach opposite scientific determinations about ARIA sufficiency in relation to NDA 208271.

In conclusion, the precedents set by PMR studies 2779-1 and 2787-1 for Movantik® NDA 204760 and SQ Relistor® NDA 021964 justify a higher standard for ARIA sufficiency. The available data, which indicates only a potential for serious risk, could justify, as a matter of policy in the Office of Surveillance and Epidemiology (OSE), a lower standard for ARIA sufficiency. Therefore, the ultimate choice between these alternative standards has policy implications, best resolved by upper level management in OSE.

Assuming ARIA insufficient for sophisticated protocol-based study of MACE risk, DEPI anticipates possible approval of NDA 208271 for oral Resistor®, with a post-marketing requirement (PMR), nearly identical in content and form to PMRs for Movantik® (NDA 204760) and SQ Relistor® (NDA 021964), as follows,

A post-marketing, observational epidemiologic study comparing Relistor (methylnaltrexone bromide) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Relistor (methylnaltrexone bromide)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among Relistor (methylnaltrexone bromide) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the Relistor (methylnaltrexone bromide)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of Relistor (methylnaltrexone bromide) exposure at the end of the study.

This determination of ARIA insufficiency does not preclude capability development research, in Sentinel, to study the validity of different methods for identifying patient populations, exposures, outcomes, or covariates relevant to PAMORA disease risks.

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/s/

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Response to Consultation Request

TO:	Dina Zand, MD, Medical Officer Division of Gastroenterology and Inborn Errors Products (DGIEP)
FROM:	Elizabeth Kilgore, MD, Medical Officer Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
THROUGH:	Joshua Lloyd, MD, Team Leader, DAAAP
THROUGH:	Ellen Fields, MD, MPH, Deputy Director, DAAAP
THROUGH:	Sharon Hertz, MD, Director, DAAAP
NDA:	208-271 Methylnaltrexone bromide (Relistor Oral)
DOCUMENT:	Supporting Document 1
APPLICANT:	Salix Pharmaceuticals, Inc.
SUBMISSION DATE:	June 19, 2015
PDUFA Date:	April 19, 2016

Overall Conclusions:

- Study 3201 was not adequately designed to fully evaluate study subjects for the presence of opioid withdrawal symptoms.
- Despite the limitations in study design for Study 3201, the identified cases of clinical events of opioid withdrawal based on Investigator and DSM-V criteria are sufficient to support the Applicant's proposed labeling.
- There did not appear to be evidence of clinically important changes in pain scores or increased daily opioid analgesic use in MNTX-treated subjects in Study 3201 as interpreted within the overall study design limitations.

Background: Methylnaltrexone (MNTX) bromide, Tradename Relistor, a peripherally acting mu-opioid receptor antagonist, was approved for administration via subcutaneous (SC) injection in 2008 under NDA 21-964 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.

Efficacy supplement 10 was submitted on June 27, 2011 to expand the indication to treatment of opioid-induced constipation in adult patients with chronic non-cancer pain. A Complete Response (CR) letter was issued on July 27, 2012. The review team concluded that although the submitted data established that Relistor 12 mg dosed once daily subcutaneously is effective for OIC in adults with chronic, non-cancer pain, there were possible safety issues related to cardiovascular adverse events and opioid withdrawal that ultimately led to the CR. This underlying concern regarding possible cardiovascular events was primarily driven by the historical context of the approval of another peripherally-acting mu-opioid receptor antagonist, Entereg, approved on May 20, 2008, for the indication of accelerating time to upper and lower GI recovery following partial large or small bowel resection with primary anastomosis. A REMS was required for Entereg designed to mitigate a serious risk, myocardial infarction (MI), because a numerical imbalance in MIs (7 vs. 0, in the context of a 2:1 randomization) had been observed in a 12-month controlled trial (b) (4)

The Applicant submitted a Formal Dispute to the CR on April 2, 2013 and a meeting was held between the Agency and the Applicant, Salix Pharmaceuticals, Inc., on May 7, 2013 where the issues raised in the Applicant's formal dispute resolution were discussed. Following that meeting, FDA concluded that additional input from an Advisory Committee was needed to review the potential for peripherally acting mu-opioid receptor antagonists to cause withdrawal symptoms, to reassess the strength of the CV signal seen with Entereg, and to advise on the potential for cardiovascular events for drugs in this class. An Advisory Committee Meeting was held in June 2014 to address the issue of a possible cardiovascular signal for the class of peripherally acting mu-opioid receptor antagonists (PAMORAs).

Dr. Julie Beitz's July 10, 2014 Appeal Response letter to the Applicant's formal dispute is summarized below in which some parts of the Applicant's dispute were granted and some were denied:

- One or more postmarketing observation studies should be conducted which could quantify the MACE risk among Relistor users in comparison to users of other treatment for OIC.

- Supplemental NDA for Relistor administered via subcutaneous injection may be approved based on existing data and Salix's request that FDA approve the supplemental NDA for Relistor based on the submitted data was granted.

- Salix should submit a complete response to the July 27, 2012 CR letter that includes proposed product labeling, a safety update, and proposal(s) for one or

more post-marketing observational cohort studies designed to assess the relative incidence of MACE among chronic non-cancer pain patients initiating Relistor via subcutaneous injection for OIC versus a comparator cohort.

The sNDA was resubmitted on July 29, 2014. On September 29, 2014 the Relistor efficacy supplement was approved with a postmarketing requirement that an observational epidemiologic study comparing Relistor (methylnaltrexone bromide) to other treatments of opioid induced constipation in patients with chronic non-cancer pain be conducted. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately.

With regard to opioid withdrawal, the general consensus from the AC meeting was that while some cases of opioid withdrawal may occur with subcutaneous Relistor, there was no definite evidence that those opioid withdrawal cases resulted in cardiovascular events.

NDA 208271 seeks approval for the use of oral MNTX 150 mg tablets (in a 450 mg daily regimen) as an alternative dosage form for Relistor subcutaneous in the treatment of OIC in patients with NCP (non-cancer pain), which is the subject of this consultative review.

Consultation Request: On August 2, 2015, DGIEP submitted a Request for Consultation to DAAAP with the following consult questions: For Study MNTX3201, determine the following:

1) Did the Applicant sufficiently assess the impact of methylnaltrexone bromide on opioid withdrawal?

2) Is there evidence of opioid withdrawal in methylnaltrexone bromide compared to placebo?

It should be noted that DAAAP previously consulted for sNDA 21964 (see DAAAP Consult dated 2/27/12 in DARRTS). DAAAP was not involved with NDA 208271 prior to this consult request.

Key Regulatory History Relevant to DAAAP Consult for NDA 208271 (Advice Under IND 67452)

- 4/2/12 - minutes for Type B Pre-NDA meeting held 3/7/12
    - You should not only record daily opioid doses administered by subjects but also capture any changes in doses that occur throughout the 12 week

double blind treatment period. In addition, you should assess pain daily using a visual analogue scale (VAS) and analyze for any correlation between the changes in opioids and pain ratings.

- 10/31/14 - Advice from DGIEP (written responses) for requested 11/4/14 meeting
    - In order for Study 3201 to support the approval of an oral Relistor formulation, the results of the pre-specified analyses supporting the proposed dose would first need to be statistically valid, allowing for the evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product.
    - The results of these key analyses of clinical endpoints considered suitable for purposes of labeling would need to be robust.**…**Note that key support for this approach would be persuasive safety data indicating that the oral formulation is better tolerated than the SC formulation (i.e., evidence that you have identified an effective alternative oral dosing formulation with evidence of improved safety compared to the available SC formulation).

Key Materials Reviewed:

- NDA 208271 relevant sections of individual Clinical Study Reports (CSRs), Summary of Clinical Safety (SCS), and Integrated Summary of Safety (ISS)
- sNDA 21964 original submission and 120-day safety update
- sNDA 21964 DAAAP Consult to DGIEP
- Advisory Committee Meeting minutes and relevant materials related to Applicant's history for sNDA 21964 and NDA 208271

Review Organization

I) Review Strategy

II) Opioid Withdrawal in Study 3201

III) Opioid Withdrawal in Other Studies Supporting Oral MNTX

IV) Opioid Withdrawal in Methadone-Maintained Subjects

V) Opioid Withdrawal in Oral MNTX Compared to Subcutaneous

VI) Postmarketing Subcutaneous Opioid Withdrawal Reports

VII) Proposed Labeling Discussion

VIII) Reviewer's Conclusions

IX) DAAAP Responses to DGIEP Questions

CONSULT REVIEW

I) Review Strategy

A total of 21 studies contributed to safety data for oral MNTX. Study 3201 was the key Phase 3 efficacy and safety study and the study for which DAAAP was consulted to assess whether the Applicant sufficiently assessed opioid withdrawal and whether there was evidence of opioid withdrawal in the MNTX-treated subjects compared to placebo.

However, in order to fully determine if, and the extent to which, oral MNTX may cause opioid withdrawal and gain an understanding of oral MNTX in an opioid-dependent population, I also reviewed 10 other studies in the submission in which oral MNTX was administered to opioid-dependent subjects, which included: 1) placebo-controlled studies, 2201, 2202, 200, and MNOC1111, 2) non-placebo-controlled study 1113, and 3) five studies conducted in methadone-maintained subjects. The remaining 10 studies were not reviewed because they were conducted in non-opioid dependent, healthy volunteers or special populations and would not contribute to an evaluation of the potential for oral MNTX to precipitate opioid withdrawal symptoms.

In all studies, my assessment of opioid withdrawal included the Applicant's findings from: 1) Opioid Withdrawal Assessment Scale scores (e.g., Objective Opioid Withdrawal Scale (OOWS) scores and Subjective Opioid Withdrawal Scale (SOWS) scores or other objective measurement tools to assess OW; 2) Pain Intensity scores; 3) MED (morphine equivalent dose) use; 4) Incidence of isolated preferred terms potentially related to opioid withdrawal, 5) Investigator-identified cases of OW and 6) DSM (Diagnostic & Statistical Manual) -V identified cases of OW. Not all studies included each of these assessments and that is noted as appropriate under the individual study discussion. A description of these assessments is discussed under the individual studies as needed. Also note that DSM-V criteria for identification of opioid withdrawal for Study 3201 was not a predefined safety endpoint or analysis in the Statistical Analysis Plan (SAP). The Applicant described the DSM-V criteria and analysis in the ISS. It is unclear whether patients were retrospectively analyzed for DSM-V criteria.

I also reviewed relevant sections of the ISS (Integrated Summary of Safety) and SCS (Summary of Clinical Safety). I found that the ISS included three DSM-V criteria subjects who were not identified in the original individual CSRs (clinical study reports)

for that study. Also, in most cases, the Applicant had not included narratives for subjects who were identified as experiencing DSM-V criteria or investigator-identified opioid withdrawal. As a result of these findings, information requests were sent to the Applicant to provide narratives for all subjects who were identified as experiencing opioid withdrawal and they complied with that request. Due to the discrepancy between the CSRs and the ISS, the Applicant's overall reports of opioid withdrawal differ from my final determination, as my review includes all cases from both the CSRs and ISS. These differences are discussed under the individual studies as needed.

Relevant studies that supported SC (subcutaneous) MNTX (i.e., Studies 3356, 3358, and 2101) were reviewed in order to provide context of the relative incidence of opioid withdrawal in SC MNTX compared to oral MNTX, although the Applicant is not proposing a labeling claim comparing the incidence of these different routes.

Note that in the Regulatory Background the meeting minutes state that the following advice was given to the Applicant: "You should not only record daily opioid doses administered by subjects but also capture any changes in doses that occur throughout the 12-week double blind treatment period. In addition, you should assess pain daily using a visual analogue scale (VAS) and analyze for any correlation between the changes in opioids and pain ratings." This advice was given to the Applicant by DGIEP. DAAAP had not yet been consulted. It is unclear why the Applicant did not follow the Agency advice to assess pain daily, as Study 3201 assessed pain at baseline (pre-and one hour post first dose), and then not again until Day 14.

Lastly, multiple oral formulations were investigated in clinical trials during the Applicant's product development. The formulation used in key Study 3201 ((b) (4)) did not use the to-be-marketed ((b) (4) formulation. However, bridging study MNOC1111, demonstrated BE between the (b) (4) and (b) (4) formulations.

II) Opioid Withdrawal in Study 3201

Study 3201: This was the key phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study which evaluated the safety and efficacy of oral MNTX 150 mg tablets versus placebo in subjects with chronic NCP (non-cancer pain) and OIC (opioid induced constipation). Participating subjects were randomly assigned to receive oral MNTX tablets as 150, 300, or 450 mg QD, or placebo QD in a 1:1:1:1 allocation ratio. Subjects underwent a 14-day screening period and a 12-week treatment period. Study drug was taken QD (daily) during the first 4 weeks; dosing was PRN during the remaining 8 weeks of the treatment period. Double-blind status was maintained throughout the course of the study.

Primary Efficacy Endpoint: The primary efficacy endpoint was the average percentage of dosing days that resulted in rescue-free bowel movements (RFBMs) within four

hours of dosing during Weeks 1-4.

Key Secondary Efficacy Endpoints (in hierarchical order)

1. Responder endpoint: Proportion of subjects who responded to study drug during Weeks 1-4, where a responder is defined as ≥3 RFBM/week, with an increase of ≥1 RFBM/week over baseline, for ≥3 out of the first 4 weeks of the treatment period.
2. Change in weekly number of RFBMs from baseline over the entire first 4 weeks (28 days) of dosing. A RFBM was defined as a bowel movement without laxative use within 24 hours prior to the bowel movement. The weekly number of RFBMs was calculated as 7 x total RFBMs in a week divided by all nonmissing assessment days.

Note that at the time of this review, DGIEP continues to have internal discussions regarding the acceptability of the Applicant's endpoints and analyses due to some changes in the Applicant's statistical analysis plan.

Patient Population and Main Inclusion Criteria: Adult men and women with a documented history of chronic nonmalignant pain (e.g., osteoarthritis, back pain, or neuropathic pain) of ≥ 2 months' duration before the screening visit were eligible to enroll. Subjects were to have been using oral, transdermal, intravenous, or subcutaneous opioids for ≥ 1 month (daily dose ≥ 50 mg of morphine equivalents per day for ≥ 2 weeks) and had a history of constipation because of opioid use for ≥ 1 month. Constipation was defined as <3 RFBMs per week on average (over the last four consecutive weeks) and one or more of the following (based upon the subject's reported history):

- Hard or lumpy stools
- Straining during bowel movements
- A sensation of incomplete evacuation after bowel movements

Objectives: The primary objective of this study was to evaluate the safety and efficacy of oral MNTX versus placebo in subjects with chronic nonmalignant pain who have OIC. The secondary objective was to determine the optimal oral MNTX dosing regimen for this indication.

Safety Assessments : Safety assessments included monitoring of adverse events (AEs), serious AEs (SAEs), and the use of concomitant treatments including opioid use and rescue laxatives; vital signs assessments; physical examination findings (including rectal examination); laboratory test results; electrocardiograms (ECGs); and results of the Objective Opioid Withdrawal Scale (OOWS), the Subjective Opioid Withdrawal Scale (SOWS), and the Pain Intensity Scale assessments.

Opioid Withdrawal Related Safety Outcomes

- Incidence of TEAEs

- Use of prior and concomitant medications
- Use of opioid medications (expressed as morphine equivalents)
- Changes from baseline in total Objective Opioid Withdrawal Scale (OOWS) score and total Subjective Opioid Withdrawal Scale (SOWS) score at each time point and end of treatment.
- Changes from baseline in pain intensity at each time point using the Numerical Rating of Pain Intensity Scale.

Safety Analyses: The safety analysis population included all randomized subjects who received ≥ 1 dose of study drug. The incidences of treatment-emergent AEs (TEAEs), SAEs, and premature study discontinuations due to AEs were tabulated by treatment group. Changes from baseline values of vital signs, clinical laboratory measures, pain scores, opioid withdrawal scores, and ECG parameters were summarized by study visit and by treatment group.

Disposition and Demographics: A total of 804 subjects with OIC and chronic, noncancer pain were enrolled and randomized to 1 of 4 treatment groups, and 803 subjects received ≥ 1 dose of study medication (201, 201, and 200 subjects in the 150, 300, and 450 mg/day groups, respectively, and 201 in the placebo group). Approximately 90% of patients in the MNTX and placebo groups completed the 4-week QD dosing period. The rate of early discontinuation from the 8-week PRN period was 12% in MNTX-treated patients and 14% in placebo-treated patients. The reasons for early discontinuation were similar across MNTX and placebo groups. The mean ages of subjects were 51 years and 53 years in the MNTX groups combined (all MNTX group) and placebo group, respectively; 62% and 65% of subjects were female, and 82% and 83% of subjects were white in the all MNTX and placebo groups, respectively.

Doses of study drug and opioid use: During the QD dosing period, the mean number of weekly doses of study drug was approximately six to seven in the MNTX and placebo groups. During the PRN dosing period, the mean numbers of weekly doses decreased in each treatment group, with comparable decreases among placebo and MNTX treatment groups. Mean weekly doses during Week 12 were 4.4 in the all MNTX group and 4.5 in the placebo group.

Efficacy Results (per Applicant): Oral MNTX demonstrated efficacy statistically superior to placebo in 2 of 3 treatment arms for the primary and key secondary efficacy endpoints. For the Primary Endpoint (average percentage of rescue free bowel movements per subject within 4 hours of all doses of study medication during the 4-week QD dosing period), statistically significant improvements were observed for the MNTX 300- and 450-mg/day groups compared to the placebo group in the intent-to-treat (ITT) population ($p = 0.0048$ and $p < 0.0001$, respectively).

Assessments of Key Opioid Withdrawal (OW) Parameters:

1) Frequency of Scheduling of Opioid Withdrawal Assessments: As shown in the table below, key OW parameters of OOWS, SOWS, and Pain Intensity Scale were conducted on days 1, 14, and 28 during the double-blind period and days 42, 56, and 84 during the prn dosing period. OOWS and SOWS were assessed pre dose and one hour post dose on Day 1. A description and results of the assessments are discussed following Table 2.

Table 2. Schedule of Assessments for Key OW Parameters (OOWS/SOWS/Pain Intensity Scale)

Study Interval	Screening Period	Double-blind Treatment Period						Follow-up visit
		Daily (QD) Dosing			As Needed (PRN) Dosing			
Study Day	-14 to -1 (± 2 days)	Day 1	Day 14 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 84 (± 2 days)	Day 98 (± 2 days)
Visit	1	2 (Baseline)	3	4	5	6	7	8
Objective Opioid Withdrawal Scale (OOWS)		X (pre and 1hr post)	X	X	X	X	X	
Subjective Opioid Withdrawal Scale (SOWS)		X (pre and 1hr post)	X	X	X	X	X	
Pain Intensity Scale		X	X	X	X	X	X	

(Protocol, Schedule of Activities)

2) Opioid Withdrawal Assessment Scales: The OOWS and SOWS are questionnaires designed to assess opioid withdrawal that results from opioid abstinence in patients who are physically dependent on opioids. See Appendix A for the original OOWS[1] , original SOWS[1], and modified SOWS used in this study. The Applicant's analysis of OOWS and SOWS were acceptable and are discussed in further detail below.

There is no total severity rating for OOWS or SOWS to categorize the opioid withdrawal as mild, moderate, or severe intensity.

a) OOWS Scores: The OOWS is a 13-item scale completed by a trained clinician. The response score for each item is 1='Present' or 0='Not Present'. Because abdominal cramping has also been identified as an AE in subjects with OIC who have been treated with MNTX, the Applicant analyzed the scores both with and without the abdominal cramping item on the scale.

Scoring of the OOWS: The maximal OOWS score is 13 if abdominal cramping item is include and 12 if abdominal cramping is not included. The total scores were calculated as follows:

[1] Handelsman, L., et al. Two new rating scales for opiate withdrawal, American Journal Drug Alcohol Abuse, 13(3), 1987, p. 293-308.

OOWS Total Score (with abdominal cramping item) = sum of non-missing scores on items 1-13 divided by number of items with a score x13. If more than 6 of 13 items had missing scores, the total score was defined as missing.

OOWS Total score (without abdominal cramping item) = (sum of non-missing scores on items 1-11 and 13 divided by the number of items with a score among items 1-11 and item 13) x 12. If more than 6 of 12 items had missing scores, the total score was defined as missing.

Overall, I found there were minimal mean changes from baseline in OOWS scores, with or without the cramping item, over the 12-week treatment period, and these changes from baseline were comparable across the placebo and MNTX treatment groups.

Table 3. Objective Opioid Withdrawal Scale Total Scores (With Cramping Item)

Assessment Time	**Placebo N=201**	**MNTX 150 mg N=201**	**MNTX 300 mg N=201**	**MNTX 450 mg N=200**
Baseline [n]	[201]	[200]	[201]	[200]
Mean (SD)	0.45 (1.118)	0.35 (1.031)	0.35 (0.836)	0.31 (0.984)
Day 1 Post Dose [n]	[201]	[198]	[201]	[199]
Mean (SD)	0.38 (0.926)	0.41 (1.113)	0.40 (0l.954)	0.35 (0.919)
Δ from BL to Day 1 Mean (SD)	-0.07 (0.629)	0.06 (0.601)	0.04 (0.635)	0.05 (0.418)
LS Mean Δ (vs Placebo)	--	0.11	0.10	0.09
Visit 3, Day 14 [n]	[190]	[187]	[187]	[181]
Mean (SD)	0.34 (0.905)	0.40 (1.013)	0.33 (0.753)	0.35 (0.841)
Δ from BL to Visit 3 Mean (SD)	-0.07 (0.720)	0.04 (0.732)	-0.02 (0.718)	0.06 (0.705)
LS Mean Δ (vs Placebo)	--	0.10	0.03	0.08
Visit 4, Day 28 [n]	[192]	[194]	[191]	[184]
Mean (SD)	0.33 (0.942)	0.39 (1.135)	0.27 (0.776)	0.32 (0.893)
Δ from BL to Visit 4 Mean (SD)	-0.10 (0.682)	0.01 (0.744)	-0.07 (0.876)	0.03 (0.557)
LS Mean Δ (vs Placebo)	--	0.08	0.00	0.08
Visit 5 , Day 42 [n]	[160]	[173]	[172]	[162]
Mean (SD)	0.40 (0.988)	0.38 (1.138)	0.20 (0.551)	0.30 (0.779)
Δ from BL to Visit 5 Mean (SD)	-0.02 (0.789)	-0.01 (0.610)	-0.13 (0.858)	-0.02 (0.595)
LS Mean Δ (vs Placebo)	--	0.00	-0.14	-0.04
Visit 6, Day 56 [n]	[154]	[169]	[165]	[159]
Mean (SD)	0.36 (0.995)	0.36 (0.973)	0.27 (0.891)	0.03 (0.670)
Δ from BL to Visit 6 Mean (SD)	-0.06 (0.734)	0.00 (0.795)	-0.08 (1.134)	0.03 (0.670)
LS Mean Δ (vs Placebo)	--	0.03	-0.05	0.05

Visit 7, Day 84 [n]	[158]	[169]	[173]	[164]
Mean (SD)	0.31 (0.836)	0.30 (1.022)	0.20 (0.513)	0.28 (0.739)
Δ from BL to Visit 7 Mean (SD)	-0.11 (0.740)	-0.09 (0.773)	-0.14 (0.819)	-0.02 (0.889)
LS Mean Δ (vs Placebo)	--	0.00	-0.08	0.02

(Applicant's table 14.3.5.1, modified by reviewer); Δ=change; BL=baseline; SD=standard deviation; LS Mean Difference (vs Placebo) is based on ANCOVA model with treatment as effect and baseline and analysis region as covariates per Applicant.

b) SOWS Scores: The original SOWS is a 16-item scale completed by the subject with individual items on the SOWS rated as 0=not at all, 1= a little, 2= moderately, 3= quite a bit, 4=extremely. In this study, the Applicant used a modified SOWS with 19 items (instead of 16 used in the original SOWS). The three items added include: 1) I have had trouble sleeping, 2) My appetite has been poor, and 3) I have had diarrhea. The other modification was that Item 16, "I feel like shooting up now" was replaced with "I have felt like taking more pain medication". In the original SOWS, the minimum possible SOWS score is 0 and the maximum is 64. For this modified SOWS, the maximum score is 76. It should be noted that this modified SOWS is the same as that used for Phase 3 studies 3356 and 3358 for subcutaneous MNTX. The use of this modified scale is acceptable since the same scale was used in all subjects in the study and scores across doses and subjects can be compared. It is unclear if the changes to the SOWS add any information with regard to determining opioid withdrawal since individual items were not analyzed for comparison across subjects or treatment groups.

Scoring of modified SOWS: The maximum SOWS score is 76 (72 if the abdominal cramping item is excluded). As with OOWS, the Applicant analyzed the SOWS scores both with and without abdominal cramping item as shown below:

> Total SOWS score (with abdominal cramping item) =sum of non-missing scores on items 1-19 divided by the number of items with a score x19. If more than 9 of 19 items had missing scores, the total score was defined as missing.
>
> Total SOWS score (without abdominal cramping item 15) = sum of non-missing scores on items 1-14, 16-19 divided by the number of items with a score among items 1-14, 16-19 x18. If more than 9 of 18 items had missing scores, the total score was defined as missing.

I found no clinically important differences in the mean changes from baseline in SOWS scores, with or without the cramping item, over the 12-week treatment period for each of the MNTX treatment groups compared to placebo to suggest a trend as shown in the table below.

Table 4. Subjective Opioid Withdrawal Scale (With Cramping Item)

Assessment Time	Placebo N=201	MNTX 150 mg N=201	MNTX 300 mg N=201	MNTX 450 mg N=200
Baseline [n]	[201]	[201]	[201]	[200]
Mean (SD)	12.71 (10.458)	11.26 (10.140)	11.06 (10.074)	9.90 (9.564)
Day 1 Post Dose [n]	[201]	[199]	[201]	[199]
Mean (SD)	7.97(9.208)	8.03(8.162)	7.60 (7.618)	6.70 (7.803)
BL Δ to Day 1 Mean (SD)	-4.73 (7.439)	-3.05 (6.655)	-3.45 (6.448)	-3.23 (5.827)
LS Mean Δ(vs Placebo)	--	1.10	0.63	0.43
Visit 3, Day 14 [n]	[190]	[187]	[187]	[182]
Mean (SD)	10.93 (8.866)	10.07 (9.275)	10.15 (9.116)	9.84 (9.235)
BL Δ to Visit 3 Mean (SD)	-1.49 (8.298)	-0.56 (6.241)	-0.94(8.725)	-0.47 (8.796)
LS Mean Δ (vs Placebo)	--	0.23	-0.05	0.16
Visit 4, Day 28 [n]	[192]	[194]	[191]	[184]
Mean (SD)	11.32 (9.223)	10.49 (9.493)	10.01 (9.346)	9.82 (10.100)
Δ from BL to Visit 4 Mean (SD)	-1.23 (8.871)	-0.32 (7.103)	-1.23 (8.546)	-0.06 (9.472)
LS Mean Δ (vs Placebo)	--	0.23	-0.55	0.14
Visit 5, Day 42[n]	[160]	[173]	[172]	[162]
Mean (SD)	10.09 (8.527)	9.86 (9.122)	9.24 (8.169)	9.62 (10.136)
Δ from BL to Visit 5 Mean (SD)	-2.48 (7.939)	-0.85 (7.078)	-1.76 (8.345)	-0.52 (9.139)
LS Mean Δ (vs Placebo)	--	0.95	0.04	1.08
Visit 6, Day 56[n]	[155]	[169]	[165]	[159]
Mean (SD)	10.40 (9.426)	9.15 (8.991)	8.96 (9.098)	8.96 (9.198)
Δ from BL to Visit 6 Mean (SD)	-2.43 (8.425)	-1.43(6.304)	-2.15 (8.664)	-0.89 (8.332)
LS Mean Δ (vs Placebo)	--	0.20	-0.45	0.47
Visit 7, Day 84 [n]	[159]	[169]	[174]	[164]
Mean (SD)	10.24 (9.007)	8.76 (9.309)	9.36 (8.946)	8.97 (9.241)
Δ from BL to Visit 7 Mean (SD)	-2.45 (9.296)	-1.56 (7.530)	-1.93 (8.744)	-1.33 (8.891)
LS Mean Δ (vs Placebo)	--	0.11	-0.19	0.11

(Applicant's table 14.3.5.2, modified by reviewer); Δ=change; BL=baseline; SD=standard deviation; LS Mean Difference (vs Placebo) is based on ANCOVA model with treatment as effect and baseline and analysis region as covariates per Applicant.

3) Pain Intensity Scale Rating and Change from Baseline in Pain Intensity: Evaluation of subjects' pain was performed using the Pain Intensity Scale. This is an 11-point rating scale ranging from 0 (None) to 10 (Worst Pain Possible), completed by the subjects based on their average pain experienced during the 24 hours prior to completing the scale.

The average pain scores at each evaluation were similar across the treatment groups, and there were minimal changes from baseline in the average scores over time

regardless of the treatment assigned. At baseline, the maximum pain scores in placebo and study drug was 10.0 and minimum was 0. I found no clinically important differences between MNTX and placebo treatment groups in the changes from baseline in pain scores. LS mean differences of pain Intensity scores from baseline compared to placebo are shown in the table below.

Table 5. Pain Intensity Scores Change from Baseline

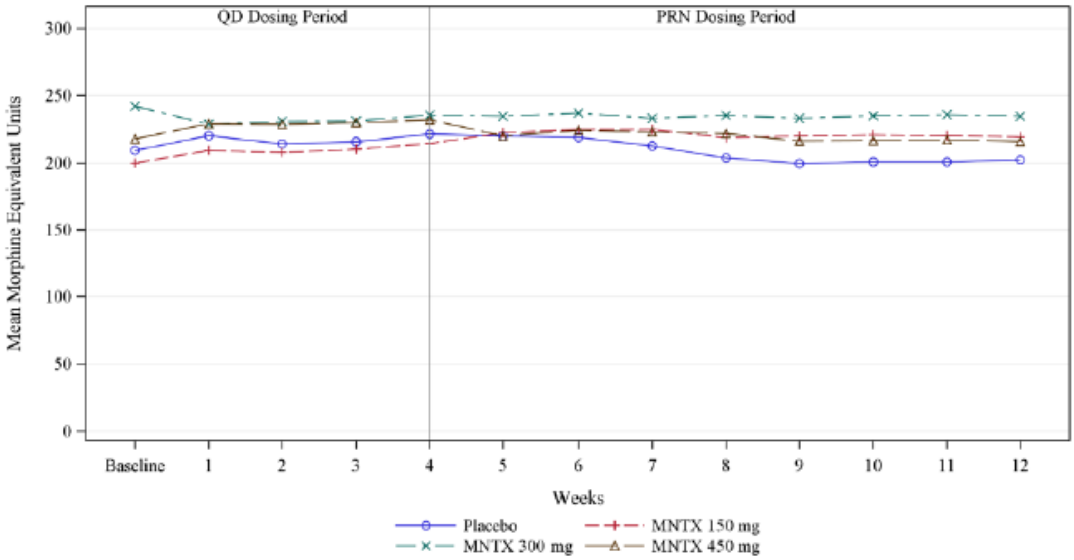
Assessment Time	**Placebo N=201**	**MNTX 150 mg N=201**	**MNTX 300 mg N=201**	**MNTX 450 mg N=200**
Baseline [n]	[201]	[199]	[198]	[198]
Mean (SD)	6.15 (2.105)	6.37 (1.846)	6.36 (1.912)	6.38 (1.870)
Visit 3, Day 14 [n]	[189]	[185]	[181]	[181]
Mean (SD)	6.12 (1.962)	6.25 (1.899)	6.23 (2.084)	6.42 (1.922)
BL Δ to Visit 3 Mean (SD)	-0.08 (1.928)	-0.14 (1.850)	-0.13 (1.517)	-0.01 (1.483)
LS Mean Δ (vs Placebo)	--	0.02	0.04	0.17
Visit 4, Day 28 [n]	[191]	[190]	[188]	[183]
Mean (SD)	6.13 (1.991)	6.38 (1.841)	6.49 (1.973)	6.33 (1.918)
BL Δ to Visit 4 Mean (SD)	-0.08 (1.984)	0.06 (1.760)	0.08 (1.654)	-0.02 (1.549)
LS Mean Δ (vs Placebo)	--	0.19	0.26	0.12
Visit 5, Day 42 [n]	[160]	[173]	[171]	[161]
Mean (SD)	6.22 (2.046)	6.36 (1.874)	6.27 (1.968)	6.35 (1.915)
BL Δ to Visit 5 Mean (SD)	-0.06 (2.079)	0.01 (1.752)	-0.13 (1.635)	-0.08 (1.666)
LS Mean Δvs Placebo)	--	0.10	0.01	0.03
Visit 6, Day 56 [n]	[155]	[169]	[163]	[159]
Mean (SD)	6.32 (1.940)	6.38 (1.861)	6.50 (1.900)	6.35 (1.994)
BL Δ to Visit 6 Mean (SD)	0.00 (2.092)	0.01 (1.817)	0.08 (1.697)	-0.05 (1.905)
LS Mean Δ (vs Placebo)	--	0.05	0.16	0.00
Visit 7, Day 84 [n]	[157]	[169]	[174]	[163]
Mean (SD)	6.21 (1.951)	6.31 (1.930)	6.45 (1.949)	6.33 (2.048)
BL Δ to Visit 7 Mean (SD)	-0.10 (2.022)	-0.04 (1.879)	0.09 (1.805)	-0.06 (1.817)
LS Mean Δ (vs Placebo)	--	0.09	0.23	0.07

(Applicant's Table 14.3.5.3, Modified by reviewer); Δ=change; LS Mean Difference (vs Placebo) is based on ANCOVA model with treatment as effect and baseline and analysis region as covariates per Applicant.

4) Morphine Equivalent Use: Mean baseline opioid use for the treatment of noncancer pain was 224 mg morphine equivalents/day, in the all MNTX group and 210 mg morphine equivalents/day in the placebo group. There were minimal changes in daily opioid use across treatment groups during the course of the study as shown in the figure and table below. However, it appears that MNTX 150 mg and 450 mg overall showed some increase in opioid use while MNTCX 300 mg showed a decrease during

the QD dosing and placebo was variable. Because the daily opioid use was not recorded in relation to pain intensity scores, (i.e., pain scores were only collected at specific time points and not daily) this information does not provide meaningful insight as to the effect of oral MNTX on analgesia.

Figure 1 . Average Daily Opioid Use



Source: Table 14.1.6.4e and Figure 14.1.2.
Abbreviations: ITT = intent-to-treat; MNTX or MOA-728 = methylnaltrexone; PRN = as needed; QD = daily; Wk = week.

(CSR, p. 69)

Table 6. Daily Opioid Use by Week – Morphine Equivalents (mg/day)

Mean by Week	Placebo N=201	MNTX 150 mg N=201	MNTX 300 mg N=201	MNTX 450 mg N=200	All
Baseline Mean SD	209.68 199.118	199.97 205.213	242.41 261.508	218.02 189.051	220.13 221.13
Week 1 [n] Mean (SD)	[201] 220.33 (234.965)	[201] 209.51 (224.639)	[199] 228.68 (230.356)	[200] 229.12 (202.318)	600 222.40 (219.253)
Week 2 [n] Mean (SD)	[201] 214.47 (219.362)	[201] 208.13 (225.054)	[198] 230.81 (231.812)	[200] 228.78 (201.853)	[599] 222.52 (219.787)
Week 3 [n] Mean (SD)	[201] 215.90 (223.815)	[201] 210.30 (226.406)	[198] 231.21 (233.077)	[198] 230.06 (206.171)	[597] 223.79 (222.037)

Week 4 [n] Mean (SD)	[199] 221.44 (238.405)	[200] 214.52 (231.085)	[196] 235.62 (234.045)	[197] 232.14 (209.612)	[593] 227.53 (225.003)
Week 5 [n] Mean (SD)	[167] 220.13 (222.540)	[177] 222.39 (267.709)	[179] 234.79 (234.604)	[169] 220.18 (206.592)	[525] 225.91 (237.684)
Week 6 [n] Mean (SD)	[167] 219.21 (221.040)	[176] 224.73 (269.057)	[178] 237.09 (235.230)	[168] 224.30 (208.773)	[522] 228.81 (239.000)
Week 7 [n] Mean (SD)	[166] 212.73 (218.865)	176 224.85 (271.326)	177 233.33 (235.544)	168 223.17 (203.235)	521 227.19 (238.408)
Week 8 [n] Mean (SD)	[161] 203.87 (200.220)	[175] 218.82 (253.436)	[174] 235.35 (236.002)	[168] 221.98 (201.558)	[517] 225.41 (231.371)
Week 9 [n] Mean (SD)	160 199.53 (201.715)	174 219.95 (256.770)	174 233.23 (236.440)	167 216.33 (200.424)	515 223.26 (232.449)
Week 10 [n] Mean (SD)	156 200.75 (205.215)	168 221.07 (262.462)	169 235.08 (239.263)	165 216.64 (204.068)	502 224.33 (236.331)
Week 11 [n] Mean (SD)	155 200.96 (203.102)	168 220.26 (261.710)	168 235.94 (243.182)	163 217.32 (202.908)	499 224.58 (237.191)
Week 12 [n] Mean (SD)	152 202.33 (203.514)	166 219.48 (261.417)	165 234.91 (243.258)	160 216.24 (203.746)	491 223.61 (237.390)

(Applicant's table 14.1.6.4e, modified by reviewer); n=number; SD=standard deviation

5) Prior and Concomitant Opioid Medications: Entry criteria for this study included current therapy with oral, transdermal, intravenous, or SC opioids for chronic nonmalignant pain for ≥ 1 month, and receiving a daily dose ≥ 50 mg of oral morphine equivalents per day for ≥ 14 days before the screening visit with no anticipated changes during the study. Almost all subjects in the study reported prior opioid use (all MNTX: 99%; placebo: 98%). It is unclear why 100% of subjects did not report prior opioid use as this was required for inclusion in the study. Use of the following medications were reported most frequently (> 15% of all MNTX or placebo subjects): oxycodone (34% vs 32%), morphine (29% vs 30%), hydrocodone/acetaminophen (27% vs 19 %), and methadone (16% vs13%).

Almost all subjects (≥ 99% in each treatment group) reported concomitant opioid use during both study periods. Oxycodone, morphine, hydrocodone/acetaminophen, and methadone were the most frequently reported concomitant opioids.

The percentages of subjects who started a new opioid medication during the QD dosing period were similar in the all MNTX group (41%) and the placebo group (40%) with the most common new opioids being oxycodone and morphine.

6) Incidence of AE Terms Potentially Related to Opioid Withdrawal

As shown in the table below, seven preferred terms in the MNTX 450 mg group had an incidence both ≥2% and greater than placebo. Of those terms, four (abdominal pain, diarrhea, anxiety and hyperhidrosis) are potentially related to opioid withdrawal. Overall, the incidence of TEAEs was slightly higher in the 450 mg group MNTX compared to placebo. The presence of these isolated preferred terms potentially related to OW do not have as much clinical importance as the presence of a cluster of terms potentially related to opioid withdrawal, but are useful to provide some understanding of the frequency of occurrence of preferred terms potentially related to OW in MNTX compared to placebo.

Table 7. TEAEs in ≥2% Subjects in the MNTX 450 mg Group with an Incidence Higher than Placebo: Oral Phase 3 Study MNTX3201

Preferred Term	MNTX 150 mg N = 201 n (%)	MNTX 300 mg N = 201 n (%)	MNTX 450 mg N = 200 n (%)	Placebo N = 201 n (%)
Abdominal Pain	11 (6)	16 (8)	21 (11)	17 (9)
Diarrhea	7 (4)	13 (7)	16 (8)	7 (4)
Headache	2 (1)	8 (4)	9 (5)	8 (4)
Abdominal distension	6 (3)	3 (2)	7 (4)	6 (3)
Anxiety	6 (3)	9 (5)	7 (4)	3 (2)
Hyperhidrosis	6 (3)	8 (4)	6 (3)	4 (2)
Blood creatine phosphokinase increased	2 (1)	1 (1)	4 (2)	1 (1)

Source: MNTX3201 Clinical Study Report, Table 14.3.1.2.1c; Abbreviations: QD = once daily; MNTX = methylnaltrexone; and TEAE = treatment-emergent adverse event.
Note: Events are sorted in descending order of frequency in the MNTX 450 mg group.

(Applicant's table, CSR, p. 18)

7) Investigator-identified Possible Opioid Withdrawal Cases: The Applicant reported no cases of investigator-identified opioid withdrawal due to MNTX in the Clinical Study Report (CSR). No placebo cases of opioid withdrawal were reported. There was one investigator-identified subject who experienced withdrawal due to alprazolam (narrative below).

Two cases of investigator-identified drug withdrawal were identified, narratives discussed below.

- Subject 102-009 (150 mg): This was a 57 year old white female with a primary pain diagnosis of multiple sclerosis (MS) that required opioids, with her entry opioid being oral hydrocodone 37.5 mg daily and was in the MNTX 150 mg treatment group. She also had a pertinent medical history of anxiety, depression, hyperlipidemia, muscle spasticity, and nausea. Relevant concomitant medications included gabapentin, baclofen, fluoxetine, alprazolam, and trazodone. She also reported use of bupropion, although the dates of use were not provided. The subject received her first dose of MNTX on 7/22/11 and her last dose on 9/25/11 with a total duration of exposure of 63 days. On (b) (6), she required hospitalization reportedly for Xanax (alprazolam) withdrawal and worsening depression (both coded as SAEs). This subject also had an SAE of hyperkalemia on 9/18/11. The narrative included details regarding the hospitalization and neurologic work-up for possible exacerbation of MS. She reportedly had been taking her alprazolam six to seven times daily instead of the prescribed dose of one mg three times daily. It was felt that the subject was having withdrawal from her alprazolam since she had not taken a dose for several hours (the narrative did not provide details or a description of possible alprazolam withdrawal but her chief complaints were numbness and tingling of bilateral upper and lower extremities for the past two weeks associated with some shortness of breath). The subject's neurologist reportedly determined that her symptoms were probably due to withdrawal from alprazolam and not an exacerbation of MS. The subject was withdrawn from the study on 10/6/11 by her request. *Reviewer's comment: The Investigator/Applicant, identified this as a case of alprazolam withdrawal. I agree with the investigator's determination as there was no description to suggest opioid withdrawal.*

Cases identified in the ISS not included in the Applicant's CSR: In the ISS, investigator-identified cases of OW included Subject 102-009, but also Subjects 009-003 (drug dependence) and 080-017 (drug withdrawal syndrome) were included in the ISS but not identified in the CSR as investigator-identified OW. In response to an IR, the Applicant provided narratives for the two subjects not previously identified. Upon my review of the narrative for subject 009-003, I determined that this case was not an Investigator-identified OW case based on the preferred terms in the narrative (narrative summarized in Table 8) but met DSM-V criteria. Subject 080-017 was investigator-identified, narrative summary below.

- Subject MNTX3201-080-017 (300 mg): This 34 year old female was taking oxycodone and Oxycontin for chronic pain. On Day 20, she was noted as

having" mild drug withdrawal syndrome" and recovered on Day 29. *Reviewer's comments: The exact terms (symptoms) of drug withdrawal were not identified in the narrative. The maximum OOWS score was 4.0 on 8/19/11 (Study Day 29); SOWS=16 on 8/19/11; Pain scores maximum 9 at Visit 7 (10/17/11).*

8) DSM-V Criteria Identified Opioid Withdrawal Cases:

Since opioid withdrawal involves a constellation of symptoms, the Applicant conducted analyses of OW by applying DSM-V criteria for opioid withdrawal, identified by the occurrence of clusters of symptoms. Subjects who met DSM-V criteria must have exhibited ≥ 3 of the following symptoms within minutes to several days (up to seven days) after administration of study drug: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, or insomnia. The analysis was performed with and without GI symptoms because these symptoms occur frequently in subjects with OIC.

The Applicant initially identified five MNTX-treated subjects who experienced possible OW based upon DSM-V criteria. No placebo cases meeting DSM-V criteria were identified. Narratives or subject ID's for the five subjects were not included in the original submission. In response to an IR, the Applicant provided the subject ID's and narratives for the five subjects identified using DSM-V criteria. Subjects included in the Applicant's response to the IR included the following: 099-011, 009-003, 148-004, 001-011, and 094-007. In the ISS, in addition to the five subjects listed in the CSR, two additional subjects were identified (001-010 and 054-017), thus making a total of seven subjects.

One subject (094-007) discontinued from the study as a result of the OW event and one subject was lost to follow up. Brief narrative summaries are discussed below:

Table 8. OW Narratives DSM-V Criteria

ID **Dose**	**Brief Narrative**
099-011 150 mg	62 year old female was taking Oxycontin (daily dose 80 mg at study entry) for osteoarthritis pain. Concomitant medications included restoril, requip, senna, Xanax, vistaril, Benadryl, ipratropium, Chantix, and Lisinopril. The subject received her first dose of study drug on 4/6/11 and last dose on 6/28/11 for a total duration of exposure of 84 days. On 5/14/11 (Day 39) the subject experienced severe AEs of **hyperhidrosis, vomiting, nausea, and diarrhea.** The outcome was resolved on 5/15/11.

	OOWS: predose =3; post dose= 2; 2; 3; 3; 2; 2 SOWS: predose= 20, post dose =24, 22, 31,20, 26, 33 (max scores on 5/4/11 and 6/29/11) Pain scores =7, 8, 7, 7, 8, 5
009-003 300 mg	46 year old male was taking oral Oxycontin (daily dose of 160 mg at study entry) and oral oxycodone (daily dose was 120 mg at study entry) for back pain. Concomitant medications included Ritalin, ibuprofen, requip, senna, Excedrin migraine, hydrochlorothiazide, dulcolax, Colace, avelox, bupropion, and amoxicillin. The first dose of study drug was on 10/14/10 and the last dose was on 1/3/11 for a total duration of exposure of 82 days. On 10/14/10 (Day 1), the subject experienced dizziness (mild), **hyperhidrosis** (mild), **nausea** (moderate), **anxiety** (mild), and investigator-identified **drug dependence** (i.e., craving more opioids). The outcome was resolved and the stop date was 10/28/10. The Applicant coded this case as an investigator identified OW case, but I determined that it instead meets the criteria for DSM-V. OOWS: predose= 0; Post dose= 0 throughout SOWS: predose =0; Post dose = 7,16, 0, 0,0, 0 (max score was on 10/27/10) Pain scores= 7, 8, 9, 8, 8, 8
148-004 300 mg	63 year old male was taking oral Dilaudid (daily dose was 32 mg at study entry) for low back pain and neck pain. The first dose of study drug was on 2/10/11 and the last dose on 5/2/11 for a total duration of exposure of 82 days. On 3/11/11 (Day 30) the subject experienced **abdominal pain upper, diarrhea,** muscle spasm, and **hyperhidrosis** all of which resolved the next day. Note that the SOWS score on 3/10/11 was 5, OOWS scores were 0, and average pain scores were stable throughout. OOWS: predose = 0; post dose = 0 throughout SOWS: predose =11; Post dose = 7; 5; 5; 4; 3; 5 Pain scores = 5, 8, 7, 7, 7, 7
001-011 450 mg	63 year old female was taking oral Percocet (daily dose 50 mg at study entry) for back pain. Pertinent concomitant medications included flexeril. On 11/3/10 (Day 29), the subject experienced **abdominal pain upper, nausea, feeling cold, restlessness, and hyperhidrosis** all of which resolved on 12/1/10. On 12/1/10, the subject also experienced restlessness and hyperhidrosis again. Hyperhidrosis was ongoing but restlessness resolved on 1/12/11. The highest SOWS score (51) was on 11/17/10.

	OOWS: predose =0; post dose= 0 throughout SOWS: predose =26; post dose =25, 24, 20, 51; 17, 26 Pain scores= 8, 8, 8, 8, 7, 6
094-007 450 mg	41 year old male was taking oral morphine (daily dose 90 mg at study entry) for back pain and prestudy opioid was morphine. Past medical and surgical history are not contributory. On 2/11/11 (Day 1), he experienced dizziness**, abdominal pain lower, tremor, hyperhidrosis, and nausea** all of which resolved on 2/12/11. This subject discontinued the study on Day 2. OOWS= 0 throughout SOWS: Visit 2 Pre dose = 2; Post dose =1. Visit 4 score= 11 Pain scores =5, 4
054-017 (150 mg)	55 year old female with underlying chronic pain for which she was taking Lortab and fentanyl who experienced mild **sinus congestion** and mild **nausea** on Day 17; mild **diarrhea** on Day 18, and **pyrexia** on Day 19. She recovered from all events except sinus congestion. No change in study dose was required and she completed the study. The maximum OOWS score was 0 and maximum SOWs score 35. OOWS= 0 throughout SOWS= 30 predose/18 post dose; subsequent post dose = 35, 35, 29, 25, 30 Pain Scores =5, 7, 6, 7, 8, 4
001-010 (450 mg)	71-year old female who experienced severe abdominal pain six days prior to treatment. On Day 4 of treatment, she experienced severe left lower **abdominal pain**, moderate **nausea**, moderate **hyperhidrosis**, and severe **diarrhea**. Study drug dose was altered due to the events. She recovered from nausea and hyperhidrosis on the same day and from diarrhea on Day 5. She did not recover from left lower abdominal pain. The last dose of study drug was on Day 10 and the subject was lost to follow up. OOWS= 0 predose and post dose SOWS= predose7/post dose 3 Pain Scores= 7

(Reviewer)

Reviewer's comments: Overall, I agree with the Applicant's findings that the incidence of OW was low. My identification of opioid withdrawal is heavily weighted on investigator and DSM-V criteria identified cases due to the limitations of the other opioid-withdrawal related outcomes (i.e., OOWS, SOWS, pain intensity scores, and

isolated preferred terms) due to study design limitations. Key findings of opioid withdrawal for Study 3201 are summarized below:

- *Key efficacy/safety Study MNTX3201 was not adequately designed to fully evaluate study subjects for the presence of opioid withdrawal because opioid withdrawal parameters of Objective Opioid Withdrawal Scale (OOWS) scores, Subjective Opioid Withdrawal Scale (SOWS) scores, and pain scores were performed too infrequently to fully capture events of opioid withdrawal. Although opioid withdrawal may occur at any time, clinically it is expected to occur within the first one to two weeks and for this reason, we recommend opioid withdrawal assessment scales be performed daily for the first seven days to two weeks. In Study 3201, these assessments were performed at baseline (pre-and one hour post first dose), and then not again until Day 14.*

- *In Study 3201, there was evidence of possible opioid withdrawal in some patients taking study drug methylnaltrexone (MNTX) based upon one Investigator-identified case of opioid withdrawal (OW) and seven cases of OW identified using DSM-V criteria.*

- *Seven preferred terms in the MNTX 450 mg group had an incidence both ≥2% and greater than placebo. Of those terms, four (abdominal pain, diarrhea, anxiety and hyperhidrosis) are potentially related to opioid withdrawal. Overall, the incidence of TEAEs was slightly higher in the 450 mg group MNTX compared to placebo.*

- *The incidence of OW was evenly distributed across dosage strengths (two 150 mg, three 300 mg, and three 450 mg). There was no dosage pattern for potential OW noted.*

- *The time to onset of OW was variable.*

- *No trends were noted with regard to use of any specific prestudy opioid for increased risk of OW in those subjects identified as having experienced possible opioid withdrawal.*

- *The patient population appeared to be on fairly high doses of opioids with relatively poorly controlled pain.*

- *There was no definite evidence of clinically important changes in Objective Opioid Withdrawal Scale (OOWS) scores, Subjective Opioid Withdrawal Scale (SOWS) scores, pain scores, or daily opioid analgesic use in MNTX -treated*

patients in Study 3201. However, due to the flaws of the study design previously described, the overall interpretability of these results is limited.

III) Opioid Withdrawal in Other Studies Supporting Oral MNTX

A) *Study 2201:* This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that used an adaptive design and evaluated placebo and four active treatment arms of oral MNTX as an IR (immediate release) tablet formulation (150, 300, 450, and 600 mg/day) in subjects with Opioid Induced Bowel Dysfunction (OIBD) and chronic noncancer pain (NCP) once daily for 28 days. OIBD includes the following: 1) Constipation (characterized by infrequent, difficult, or incomplete bowel movements, straining and hard, dry stools) and 2) The broader constellation of adverse GI effects associated with opioid therapy such as abdominal cramping, bloating, nausea, and loss of appetite. The primary objective of the study was dose response relationship and safety. There were 33 placebo and 89 MNTX- treated subjects. OOWS, modified SOWS, and pain intensity scores were obtained at BL (baseline), Day 1 (pre and post dose), Days 7, 14, 28, and 42 (follow up). I reviewed the line listings for OOWS and SOWS scores with particular attention to Day 7 to see if there were any patterns suggesting higher scores around Day 7 than subsequent days. Overall, I saw no patterns to suggest opioid withdrawal events. There was no evidence of clinically important increases in OOWS, SOWS, or mean pain intensity scores in any treatment group. There were no reports of investigator identified opioid withdrawal events. There was no mention in the report that a DSM-V analysis was conducted. *Reviewer's comments: There was no definite evidence of opioid withdrawal in the IR tablet formulation of oral MNTX in this particular study.*

B) Study 2202: This was the same study design and patient population as Study 2201. There were 99 MNTX and 29 placebo subjects who received the same doses of MNTX as Study 2201, but with an (b) (4) capsule formulation. An abbreviated CSR was submitted which did not include a summary table for OOWS, SOWS, or pain intensity scores. However, individual line listings (Listing 16.2.6.2 and 16.2.6.3) were included for OOWS and SOWS, respectively. A line listing of pain intensity scores was not included in the submission. There were no major trends in OOWS/SOWS scores or changes to suggest clinically important opioid withdrawal. There were two reported cases of possible drug withdrawal syndrome, one investigator identified (Subject 001173) and one DSM-V identified (Subject 001396). Note that neither of these cases was specifically identified as such in the CSR, but were identified by the Applicant in the ISS. In response to an IR, the Applicant provided the narrative for Subject 001173. The narrative for Subject 001396 was already provided in the ISS. Both narratives are summarized below:

- Subject 2202-027-001173 (600 mg MNTX): 46 year old male was taking methadone and bupropion for chronic pain. On Day 6, he experienced "mild drug withdrawal syndrome". He recovered on Day 8, required no treatment, and continued in the study without dose adjustment.

- Subject 2202-032-001396 (600 mg MNTX): 60 year old woman with type 2 diabetes and other medical conditions who experienced abdominal cramping and nausea after her first dose of 600 mg MNTX. Within hours, vomiting became severe and the subject presented to the emergency department where she was hospitalized and given a diagnosis of gastroenteritis. She was treated medically and symptoms resolved within 48 hours. She withdrew from the study. The possible OW terms of abdominal cramping, nausea, and vomiting are all GI-related.

Reviewer's comments: There were two reported cases of possible OW in this study which used the MNTX (b)(4) *capsule. It is unclear how possible OW seen with the capsule formulation relates to the potential for OW with the TBM formulation.*

C) Study 200: This was a Phase 2, randomized, double-blind, parallel-group, placebo-controlled study in 192 MNTX in doses of 10, 50, 150, 300, and 450 mg and 44 placebo patients with OIBD (opioid-induced bowel dysfunction) and chronic noncancer pain enrolled for 28 days (double-blind) with a14 day follow up. This was considered a dose response relationship and safety study to determine the appropriate doses for Phase 3. OW assessments included OOWS, SOWS, TEAEs, and concomitant treatments including opioid use. Pain intensity scale assessments were made daily, and a Brief Pain Inventory (Short Form) was completed at baseline and Days 14 and 28. This study was terminated because of lack of efficacy. The Applicant submitted an abbreviated clinical study report which included data on demography, discontinuations, safety and limited efficacy findings. In the abbreviated CSR, no OOWS/SOWS scores or pain intensity scores were reported, although the Applicant included scores from this study in the pooled placebo-controlled studies. The most frequently occurring GI disorders were nausea (5%), abdominal pain and flatulence (4% each), and diarrhea and vomiting (3% each). The narrative (provided by the Applicant in response to an IR) for the one DSM-V criteria identified case of OW (identified in the ISS) is as follows:

- MOA7280200-115-5835 was a 52-year old white male who was taking oxycodone for non-cancer pain. On Day -13 (predose), the subject experienced mild bronchitis. On Day 16 post dosing, he experienced pyrexia and on Day 17, diarrhea and vomiting. He recovered from all events on Day 20.

Reviewer's comments: This study identified one case of DSM-V criteria possible OW. Most of these terms, however, were GI-related and the pryrexia may have been due to an underlying bronchitis. Therefore, although this case is included as a possible OW, the narrative does not provide strong support.

D) Study MNOC1111: This Phase 1B study included an open-label, single dose of SC MNTX followed by a double-blind, randomized, placebo-controlled single dose of 450 mg of MNTX (3x150 mg) [redacted] tablets, 450 mg MNTX [redacted] tablets, or matching placebo. The population included chronic non-cancer pain patients with OIC. The primary objective was to evaluate the PK and efficacy of oral [redacted] formulated MNTX tablets. Subjects were required to be taking a prescribed minimum opioid dose of 80 mg oral morphine equivalents (including methadone) per day for at least 14 days prior to Day -4 (open-label phase) and for the duration of the study. The open-label phase consisted of a single 12 mg subcutaneous dose of MNTX. The double-blind phase consisted of responders from the open-label phase who were randomized to receive a 450 mg single dose of [redacted] MNTX formulation or [redacted] MNTX formulation.

This study was conducted to assess whether 150 mg tablets manufactured using a [redacted] method exhibited the same safety and efficacy outcome as was observed with the [redacted] manufactured tablets. In study MNPK1001, statistical pharmacokinetic bioequivalence was demonstrated between single 450-mg doses of the [redacted] tablets and [redacted] tablets in healthy human subjects. The dose of 450 mg (3 x 150 mg tablets) was selected to match the most effective oral dose of MNTX from study MNTX-3201.

Opioid Withdrawal Assessments: Serial assessments of COWS, SOWS, investigator determination of OW by DSM-V and pupillometry were performed at predose of the oral dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours following the double-blind dose of study drug to evaluate opioid withdrawal. The COWS (see Appendix B) total score severity categories are < 5 = none, 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; > 36 = severe withdrawal. The SOWS total score severity categories are 0 = none; 1-10 = mild; 11-20 = moderate; 21-30 = severe. In addition, the question “Based on the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria, did this subject experience opioid withdrawal?” was answered ‘yes’ or ‘no’ by a trained and blinded investigator familiar with opioid withdrawal symptoms.

Results: A total of 128 subjects were enrolled in the study. Of the 120 responders, 112 entered the double-blind phase and were randomized to treatment with study drug (37 placebo, 38 [redacted] 37 [redacted] A total of 111 subjects completed the study (one subject was lost to follow-up). Opioid withdrawal results were analyzed descriptively. Overall, the COWS and SOWS scores were low and there were minimal changes from baseline (i.e., before the oral dose) at time points up to 12 hours post dose for the placebo and oral MNTX groups in the double-blind period. The observed changes from baseline were similar between placebo and oral MNTX treatment groups. For example, mean changes from baseline in COWS score at the 2-hour postdose time point were 0.00, -0.24, and -0.16 in the placebo, [redacted] MNTX, and [redacted] MNTX groups, respectively.

The numbers and percentages of subjects by COWS and SOWS total score severity grade were determined. All subjects had severity grades of none or mild for COWS and SOWS scores during the double-blind period, and there were no notable differences among placebo and oral MNTX groups in the percentages of subjects by COWS and SOWS severity grades.

Table 9. Opioid Withdrawal Severity Based on COWS After the Double-Blind Single Oral Dose by Treatment and Timepoint

Assessment Time COWS Severity	DB Placebo (N=37)[%]	DB (b) (4) MNTX 450 mg (N=38)[%]	DB (b) (4) MNTX 450 mg (N=37) [%]
Baseline			
None	36 [97]	36 [95]	36 [97]
Mild	1 [3]	2 [5]	1 [3]
0.5 h Post- Dose			
None	37 [100]	37 [97]	37 [100]
Mild	0	1 [3]	0
1 h Post-Dose			
None	37 [100]	38 [100]	37 [100]
1.5 h Post-Dose			
None	37 [100]	38 [100]	37 [100]
2 h Post- Dose			
None	37 [100]	37 [97]	37 [100]
4 h Post Dose			
None	37 [100]	38 [100]	37 [100]
6 h Post- Dose			
None	37 [100]	38 [100]	36 [97]
8 h Post -Dose			
None	37 [100]	37 [97]	37 [100]
Mild	0	1 [3]	0
12 h Post-Dose			
None	37 [100]	38 [100]	37 [100]

Note: COWS=Clinical Opiate Withdrawal Scale; DB = Double-Blind; (b) (4)
Note: Severity is determined based on COWS total score: 5-12=mild; 13-24=moderate; 25-36=moderately severe; More than 36=severe withdrawal.

(Applicant's Table 14.2.11, modified by reviewer, Protocol MNOC1111)

The Applicant found that no subject in the oral MNTX treatment groups experienced opioid withdrawal based on the DSM-V criteria or as determined by the investigator at post-baseline time points. I found one subject (Subject 0014-0011, 450 mg (b) (4) who experienced mild nausea, abdominal pain, and vomiting on Day 1. However, all of these terms are GI-related, and in my opinion, this case is equivocal and should not be considered as an OW case since it is impossible to determine whether these terms were due to OW or GI effects from the drug. The subject recovered the same day.

TEAEs occurring in ≥2 subjects potentially related to OW of abdominal pain upper, nausea, and vomiting all occurred with a much higher incidence in (b) (4)

[redacted] than [redacted] as shown in the table below.

Table 10. TEAEs Occurring in ≥ 2 Subjects by System Organ Class and Preferred Terms in the Double-Blind Period (Safety Population) Study MNOC1111

	Placebo (n = 37)	[redacted] MNTX 450 mg (n = 38)	[redacted] MNTX 450 mg (n = 37)	All Subjects (N = 112)
Subjects with any TEAE	8 (21.6)	12 (31.6)	6 (16.2)	26 (23.2)
Gastrointestinal disorders				
Abdominal pain	0	1 (2.6)	1 (2.7)	2 (1.8)
Abdominal pain upper	0	2 (5.3)	1 (2.7)	3 (2.7)
Nausea	1 (2.7)	4 (10.5)	1 (2.7)	6 (5.4)
Vomiting	0	3 (7.9)	1 (2.7)	4 (3.6)
Investigations				
Heart rate increased	2 (5.4)	2 (5.3)	2 (5.4)	6 (5.4)
Musculoskeletal and connective tissue disorders				
Musculoskeletal discomfort	0	3 (7.9)	0	3 (2.7)
Nervous system disorders				
Dizziness	0	2 (5.3)	0	2 (1.8)
Headache	3 (8.1)	3 (7.9)	1 (2.7)	7 (6.3)
Respiratory, thoracic and mediastinal disorders				
Rhinorrhea	1 (2.7)	1 (2.6)	1 (2.7)	3 (2.7)
Yawning	1 (2.7)	1 (2.6)	0	2 (1.8)

Source: Table 14.3.1.2a.
Abbreviation: Abbreviations: [redacted] MNTX = methylnaltrexone; TEAE = treatment-emergent adverse event; [redacted]
Note: Adverse events are coded using MedDRA version 15. A subject reporting more than one TEAE for a particular preferred term or system organ class was counted only once for that term or class at the greatest intensity. Adverse events are presented in the treatment arm the subject was on when the event started. The treatment was determined by comparing the start dates of the treatment to the onset date of the adverse event.

(Applicant's table, CSR, p. 58-59)

Reviewer's Comments: Limitations of this study include the following: 1) Pain intensity scores and morphine equivalent dose use were not recorded; 2) The duration for monitoring was only 12 hours post dose. An advantage, however, is that the COWS was used as the objective opioid withdrawal tool. COWS is preferred to OOWS since the COWS provides a severity scale for scores, unlike the OOWS, for which a severity scale for scores has not been established. No subject had a COWS score of moderate or severe rating. There was a higher incidence of GI-related AEs in the [redacted] compared to the [redacted] However, an isolated increased incidence of a single GI-related term potentially related to OW does not necessarily correspond to an increased clinical presentation of opioid withdrawal. There does not appear to be an increased incidence of OW (based on investigator or DSM-V criteria) in one formulation compared to the other. No subject had a COWS score greater than mild severity.

E) Study 3200A3-1113-US: This was a PK study for the 150 mg IR (immediate release tablet), or 150 mg [redacted]) tablet, or a single 450 mg dose of oral MNTX in 65 subjects with chronic NCP and OIC. Part 1 was a randomized, open-label,

single-dose, two-period, four-sequence, crossover study design and Part 2 was an open-label, single-dose, single-period, single-sequence design. There were no formal assessments or analyses for opioid withdrawal. Twenty-one (32%) subjects experienced TEAEs. The most frequent AEs were nausea and headache.
Reviewer's comments: This study was not placebo-controlled and there were no formal assessments for OW. I reviewed the AEs for terms potentially related to OW and found no definite evidence of opioid withdrawal cases.

IV) Opioid Withdrawal in Methadone-Maintained Subjects

In the studies conducted in methadone-maintained subjects, OW was assessed using the modified Hiimmelsbach, OOWS, SOWS, and pupillometry. The modified Himmelsbach (mHS) objective opioid withdrawal scale includes assessments of yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, restlessness, vomiting, nausea, and diarrhea using the following scores: 1 = none, 2 = mild, 3 = moderate, and 4 = severe.

Because there is no clinical correlate with regard to pupillometry and OW, pupillometry results will not be discussed in this review. In the discussion below, DWS=drug withdrawal syndrome and may be used interchangeably with opioid withdrawal/opioid withdrawal syndrome (OW/OWS).

A) Study 102 (N=28 MNTX; 27 placebo): This was a randomized, double-blind, four-period, cross-over, placebo-controlled study using MNTX 50 or 150 mg (b) (4) capsules or placebo with a daily dose of 50, 150, or 450 mg or placebo per period. The primary objective of the study was to assess the effect of a single oral dose of MNTX on oral-cecal transit time. The modified Himmelsbach showed no patterns to suggest clinically important opioid withdrawal overall. Two subjects (7%) were identified with the AE term opioid withdrawal syndrome during treatment periods with MNTX and one of these subjects experienced two episodes of withdrawal. The most frequent TEAEs overall were headache (36%), nausea (32%), flatulence (21%), upper abdominal pain (14%) and abdominal pain (11%), dizziness (14%), and restlessness (11%).

- Subject 102-001-0000014: Onset of moderate OW approximately 23 hours after the first dose of MNTX 450 mg. The symptoms resolved after 30 minutes. Specific symptoms were not described.

- Subject 102-001-0000015: Onset of OW approximately 17 hours after the third dose of MNTX 450 mg and resolved in approximately three hours. The second episode occurred approximately four days after the third (final) dose of MNTX

150 mg and resolved in approximately 27 hours. Specific symptoms were not described. Both events were considered mild.

B) Study 105 (N=24 MNTX): This was a randomized, open-label, three-period cross over study to determine the relative BA of two oral formulations of MNTX and to compare the PD of the two oral formulations to the subcutaneous formulations. Oral doses and formulations were MNTX 150 mg tablet and MNTX 150 mg (b) (4) capsule (300 mg). Subcutaneous MNTX injection dose was 0.15 mg/kg. Subjects received three doses of treatment with each dose separated by a washout of ≥7 days. The modified Himmelsbach and pupillometry were used before and after test article administration on day one and on another day when the test article was not administered to evaluate reported symptoms of methadone withdrawal. One subject (105-001-000008) withdrew due to AE of drug withdrawal syndrome; one withdrew due to vomiting; and one due to "behavior inconsistent with protocol requirements." The most frequent TEAEs were abdominal pain (62%), drug withdrawal syndrome (54%), nausea (42%), headache (37%), back pain (25%), constipation (21%), and hyperhidrosis (12%). Of the 13 subjects who experienced DWS, 12 experienced AEs after receiving MNTX in the subcutaneous formulation and one subject after capsule formulation. The events of DWS were considered severe by the investigator in five subjects and moderate in eight subjects. Of the 13 subjects who experienced an AE of DWS, seven had Himmelsbach performed during the AE. No increase in the modified Himmelsbach Scale (mHS) was observed in six of the seven subjects. With regard to AE terms potentially related to opioid withdrawal, three (12%) subjects experienced AEs of hyperhidrosis that began within 46 minutes after receiving MOA-728 in the subcutaneous formulation. The one subject who experienced OW after the oral formulation is summarized below:

- Subject 105-001-000008: This was a 49 year old male who received 300 mg of MNTX in period 1 in a tablet, followed by 300 mg of MNTX in period 2 in a capsule. The subject experienced abdominal cramping, vomiting, chills, and diarrhea that started approximately two hours after administration of the MOA-728 capsule formulation and resolved in approximately five hours. The subject was discontinued prior to administration of MNTX in the subcutaneous formulation. The total Himmelsbach score was 8 predose and increased to 12 postdose (five hours after administration of MNTX).

C) Study 1109 (N=20 MNTX; 5 placebo): This was a randomized, double-blind, two ascending single-doses, cross-over, placebo- controlled PK study of MNTX 150 mg capsules or placebo given as 150 mg MNTX, then 450 mg, or placebo. The modified Himmelsbach Scale was used to assess methadone withdrawal two hours predose and five hours postdose. Changes in scores for all subjects were equal or less than one unit for each of the individual subscales. During the study, 18 (72%) subjects experienced

at least one TEAE. The most frequent TEAEs included abdominal pain (40%), nausea (24%), and headache (20%). Overall, there did not appear to be trends for the mHS scores. No subject was specifically identified as experiencing DWS.

D) Study 1111 (N=28 MNTX; 28 Placebo): This study was to assess the effect of a high fat meal and compare MNTX 150 mg IR tablet with capsule or placebo. This was a randomized, single-blind, four-period, four-sequence cross-over, placebo-controlled study with eight doses of treatment (two doses per period administered on Days 1 and 2 separated by a 7 day washout). Pupillometry was performed but mHS or other opioid withdrawal assessments were not performed. Based on my review, AE terms suggestive of OW included palpitations, lacrimation increased, abdominal pain, abdominal pain upper, nausea, vomiting, chills, feeling cold, feeling hot, feeling jittery, feeling body temperature change, arthralgia, muscle twitching, pain in extremity, tremor, nervousness, cold sweat, hyperhidrosis, rhinorrhea, piloerection, hot flush, and heart rate increased. Chills, feeling cold, feeling jittery, feeling body temperature change, cold sweat, and piloerection occurred only in the MNTX-treated group, but all others occurred in both placebo and MNTX. While there may have been some AE terms suggestive of OW, no formal assessments of opioid withdrawal were conducted. However, the presence of AEs terms suggestive of opioid withdrawal suggest that there may have been some subjects who experienced at least some symptoms of opioid withdrawal, although an exact incidence cannot be determined.

E) Study 1115 (N=26 MNTX; 2 placebo): Pupillometry was assessed but other measures of opioid withdrawal were not included in the study design. Twenty-five (89%) subjects experienced treatment-emergent adverse events (TEAEs). Of these subjects 92% had one or more TEAEs after receiving MOA-728 in the (b) (4) tablet formulation, 80% after receiving MOA-728 in the IR tablet formulation, and 45% after receiving placebo. The most frequent TEAEs were abdominal pain, nausea, headache, vomiting, rhinorrhea, and hyperhidrosis. No specific cases of withdrawal were identified. While there may have been some AE terms suggestive of OW, no conclusions about opioid withdrawal can be made based on this study.

Reviewer's Comments: Across all studies conducted in methadone-maintained subjects, 15 subjects (12%) were identified as experiencing OW. Of the 15 subjects, 12 experienced OW after the subcutaneous route compared to only three who received an oral formulation of MNTX. No cases of OW were identified in placebo. This suggests that in methadone subjects, the subcutaneous MNTX has a higher risk of OW than oral. The highest incidence of OW was in Study 105. The generalizability of the findings from Study 105, however, is limited due to the small sample size (i.e., 24 MNTX subjects) with no placebo for comparison, and this patient population (i.e., methadone-maintained) may differ from patients taking opioids for chronic non-cancer pain.

V) Opioid Withdrawal in Oral MNTX Compared to Subcutaneous MNTX

Studies Contributing to Subcutaneous Safety

Three studies contributed to the evaluation for the potential of SC MNTX to cause OW which included Studies 3356, 3358, and 2101. All studies used SOWS, OOWS, pain intensity scores, and morphine equivalent opioid use as measures for opioid withdrawal. Studies 3356 and 3358 have been previously reviewed by DAAAP (see DARRTS 2/27/12). I reviewed the DAAAP consult for NDA 21964 as well as the Applicant's summarized findings related to opioid withdrawal from the 120 day update as presented in the ISS for this NDA. Key features of the studies and key OW results are summarized below:

- Study 3356 was a phase 3, international study conducted at 91 sites in subjects with chronic, NCP and OIC. After a screening period, eligible subjects were randomized to SC MNTX 12 mg QD, SC MNTX 12 mg QOD, or placebo in a 1:1:1 ratio. Subjects in all 3 treatment groups received daily blinded SC injections. Within the MNTX QOD group, subjects received alternating MNTX QOD (beginning on Day 1) and matching placebo QOD (beginning on Day 2). Following completion of the 4-week (double-blind) period, subjects continued treatment with SC MNTX 12 mg PRN, but no more than QD, for 8 weeks of open-label treatment. The primary objective of this study was to evaluate the safety, efficacy, and tolerability of SC MNTX 12 mg compared with placebo in this patient population. The study was completed in November 2008. There were 150 subjects who received MNTX QD, 148 MNTX QOD, and 162 placebo. Seven MNTX subjects were identified in the DAAAP Consult who experienced possible clinically important opioid withdrawal using a retrospectively applied criteria as follows: 1) OW which may have resulted in study discontinuation using the DSM-IV criteria of Adverse Events consistent with opioid withdrawal which include the presence of three of more of the following: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; insomnia and with a reviewer criteria of ≥3 of the DSM-IV preferred terms occurring on the same day, or 2) cases of Investigator identified Drug Withdrawal Syndrome. Interpretation of the study results were limited due to flaws in the study design, primarily the infrequent assessments of OOWS, SOWS, and pain intensity scores.

- Study 3358 was a multi-center, open-label, phase 3 study in subjects with NCP and OIC conducted at 120 investigational sites. Subjects who participated in this study had a history of chronic, NCP and OIC for ≥ 2 months prior to the screening visit. After a 2-week screening period, subjects who met entry criteria

received SC MNTX QD during the 48-week treatment period. All subjects (N=1034) received open-label SC MNTX 12 mg, with instructions to administer MNTX daily. MNTX dosing frequency was adjusted to range between no more than one dose daily and not less than one dose per week. In the DAAAP consult, eight MNTX subjects with possible OW were identified using the same criteria of OW determination as was used for Study 3356. The same study design flaws were noted in this study as were for Study 3356, in addition to the fact that 3358 was an open-label study.

- Study 2101 was a multicenter, double-blind, randomized, placebo-controlled phase 2 study of SC MNTX 12 mg QD in the treatment of OIC during rehabilitation after orthopedic procedures. Subjects, who had undergone orthopedic procedures within the previous 4-10 days and met entry criteria, were randomly assigned to receive either MNTX 12 mg QD or placebo for 4 to 7 days. Subjects were required to discontinue all laxative therapy (with the exception of stool softeners) for 48 hours prior to the first dose of study drug; subjects who required rescue laxative medications during the study were considered treatment failures and discontinued from the study. The objectives of this study were to evaluate the safety and efficacy of SC MNTX 12 mg in a population of patients with OIC following orthopedic surgery. The study was completed in January 2009. A total of 33 subjects were treated with either MNTX (n=18) or placebo (n=15) and were included in the statistical analyses. Twenty-seven (27) subjects (82%) completed the study. Subjects who participated in this study had undergone an orthopedic procedure (i.e., total knee or hip replacement, spinal fusion, or reduction of fracture[s] with or without surgical fixation post trauma), received opioid analgesics after the procedures, and were expected to require daily opioid analgesics for ≥ 7 days after randomization. The Applicant reported that OW results from this study for the pain scores, OOWS, and SOWS for both treatment groups **s**howed that the ratings for pain demonstrated no increase from baseline to day 1 post-dose or to end-of-study and no difference in pain scores between the treatment groups. Interpretation of the SOWS and OOWS data was limited by the considerable percentage of subjects with scales not assessed in both treatment groups across all time points. Nonetheless, review of the SOWS and OOWS results showed no consistent patterns to suggest increases over time and no clinically important difference was noted in the scores between treatment groups. For daily opioid use, during the first three days of study drug dosing, the median opioid use was similar between the two groups, and the dosing ranges showed a large degree of variability. After day four, the number of subjects in both groups is too small to detect a difference. I reviewed Study 2101 with regard to OW and agree with the Applicant's results that no cases of clinically important opioid-withdrawal were identified, with limitations as noted above.

Oral Placebo-Controlled OIC Pool vs Subcutaneous Placebo-Controlled Pool (TEAEs Potentially Related to OW)

The incidence of TEAES potentially related to OW in MNTX-treated subjects in the Oral Placebo-controlled OIC pool (450 mg QD group) compared with MNTX-treated subjects in the SC placebo-controlled OIC pool (12 mg QD/QOD) is shown in the table below. The rate per 100 Person Years (PY) was lower for oral treatment compared with the subcutaneous route for each event. The number of subjects (N=316) for the subcutaneous placebo-controlled pool consisted of 298 MNTX-treated subjects from Study 3356 and 18 MNTX-treated subjects from study 2101. As shown, the incidence of events for the SC MNTX pool was higher than or equal to the oral groups for each event listed.

Table 11. Incidence Rate of TEAEs Potentially Associated with Opioid Withdrawal Symptoms: Oral Placebo-Controlled OIC Pool vs Subcutaneous Placebo-Controlled Pool

	Subjects With NCP and OIC			
Preferred Term	SC MNTX 12 mg (N=316) (PY=21.0) n (%) [Rate per 100 PY]	Oral MNTX 450 mg (N=385) (PY=46.0) n (%) [Rate per 100 PY]	Oral MNTX All doses (N=1057) (PY=144.0) n (%) [Rate per 100 PY]	Oral Placebo (N=344) (PY=45.1) n (%) [Rate per 100 PY]
Abdominal pain	54 (17) [290.9]	30 (8) [69.7]	68 (6) [50.0]	20 (6) [46.3]
Nausea	32 (10) [164.2]	21 (6) [46.7]	68 (6) [49.3]	23 (7) [53.4]
Diarrhea	27 (9) [137.2]	21 (6) [46.7]	49 (5) [34.9]	10 (3) [22.5]
Hyperhidrosis	18 (6) [89.4]	6 (2) [13.3]	24 (2) [17.0]	5 (2) [11.2]
Vomiting	13 (4) [63.2]	16 (4) [35.3]	32 (3) [22.5]	12 (4) [27.1]
Abdominal pain upper	10 (3) [49.1]	12 (3) [26.6]	23 (2) [16.2]	8 (2) [18.3]
Hot flush	9 (3) [43.8]	3 (1) [6.6]	8 (1) [5.6]	4 (1) [8.9]
Tremor	7 (2) [33.9]	4 (1) [8.7]	18 (2) [12.7]	1 (< 1) [2.2]
Anxiety	5 (2) [24.2]	7 (2) [15.5]	23 (2) [16.3]	3 (1) [6.7]
Rhinorrhea	5 (2) [24.3]	8 (2) [17.8]	18 (2) [12.7]	4 (1) [8.9]
Piloerection	5 (2) [24.1]	0	1 (< 1) [0.7]	0
Chills	5 (2) [23.9]	4 (1) [8.8]	7 (1) [4.9]	0
Restlessness	3 (1) [14.4]	2 (1) [4.4]	11 (1) [7.7]	2 (1) [4.4]

Source: ST1.5.3.1, ST8.5.3.1, and Supplemental Tables 1 and 2; Abbreviations: NCP = non-cancer pain, OIC = opioid-induced constipation; MNTX = methylnaltrexone; PY = person years of exposure; QD = once daily; and QOD = every other day.

(ISS, p. 98)

Reviewer's comments: The incidence of AE terms potentially related to OW was considerably higher for the following terms in SC vs oral 450 mg: abdominal pain (17% SC vs 8% oral MNTX), nausea (10% SC vs 6% oral), hyperhidrosis (6% SC MNTX vs 2% oral) and diarrhea (9% SC vs 6% oral). This table compares all oral placebo-controlled OIC pool and SC pool. As has been previously noted, the incidence of isolated preferred terms potentially related to OW does not necessarily correlate to a clinical presentation of opioid withdrawal syndrome. Therefore, these findings cannot be used to make a conclusion about the incidence of OW in SC versus oral MNTX.

Double-Blind Subcutaneous MNTX (Study 3356) vs Oral MNTX (Study 3201)

The table below presents a summary of all TEAEs that occurred in ≥2% of subjects and more frequently in MNTX than in placebo in the key Phase 3 double-blind Studies 3356 (SC MNTX) and key phase 3 Study 3201 (oral MNTX). For Study 3356, only the four-week, placebo-controlled treatment period is presented. For oral Study 3201, the first four weeks are presented for comparison as well as the full 12 week treatment. During the four-week period, TEAEs that occurred more frequently in SC than oral included abdominal pain, nausea, diarrhea, hyperhidrosis, and hot flush. Events more frequent with oral MNTX compared to SC were abdominal distension, vomiting, rhinorrhea, and blood creatinine phosphokinase increased. All of these terms except creatinine phosphokinase are potential OW terms.

Table 12. TEAEs that Occurred in ≥2% of Subjects and More Frequently in the MNTX Treatment Group than Placebo in SC MNTX Study 3356 and Oral MNTX Study 3201

	SC MNTX Study 3356 – double-blind, placebo-controlled period – 4 weeks		Oral MNTX Study 3201 – double-blind, placebo controlled periods – 12 weeks total, including 4 weeks QD plus 8 weeks PRN dosing			
Preferred Term	SC MNTX 12 mg QD – 4 weeks[a] N = 150 n (%)	SC Placebo QD – 4 weeks[a] N = 162 n (%)	Oral MNTX 450 mg QD – 4 weeks[b] N = 200 n (%)	Oral placebo QD – 4 weeks[b] N = 201 n (%)	Oral MNTX 450 mg – 12 weeks[c] N = 200 n (%)	Oral placebo – 12 weeks[c] N = 201 n (%)
Abdominal Pain	29 (19.3)	6 (3.7)	18 (9.0)	12 (6.0)	21 (10.5)	17 (8.5)
Nausea	13 (8.7)	10 (6.2)	9 (4.5)	11 (5.5)	12 (6.0)	18 (9.0)
Diarrhea	9 (6)	6 (3.7)	9 (4.5)	4 (2.0)	16 (8.0)	7 (3.5)
Hyperhidrosis	9 (6)	2 (1.2)	5 (2.5)	2 (1.0)	6 (3.0)	4 (2.0)
Headache	6 (4.0)	4 (2.5)	8 (4.0)	4 (2.0)	9 (4.5)	8 (4.0)
Hot Flush	4 (2.7)	3 (1.9)	2 (1.0)	2 (1.0)	2 (1.0)	4 (2.0)
Abdominal distension	1 (0.7)	1 (0.6)	7 (3.5)	4 (2.0)	7 (3.5)	6 (3.0)
Vomiting	1 (0.7)	8 (4.9)	6 (3.0)	3 (1.5)	7 (3.5)	9 (4.5)
Rhinorrhea	2 (1.3)	2 (1.2)	4 (2.0)	1 (0.5)	4 (2.0)	3 (1.5)
Anxiety	3 (2.0)	3 (1.9)	3 (1.5)	1 (0.5)	7 (3.5)	3 (1.5)
Blood creatine phosphokinase increased	0	0	1 (0.5)	0	4 (2.0)	1 (0.5)

Source: Relistor Prescribing Information; Study 3201 (In-text Table 25) CSR.
[a] Events reported during 4 weeks of double-blind, placebo-controlled QD dosing in Study 3356.
[b] Events reported during 4 weeks of double-blind, placebo-controlled QD dosing in Study 3201.
[c] Events reported during 12 weeks of double-blind, placebo-controlled treatment in Study 3201: 4 weeks of QD dosing plus 8 weeks of PRN dosing.

(Applicant's table, SCS p. 66)

Reviewer's comments: In the four-week double-blind period, AE terms potentially related to OW with an incidence ≥2% occurred with a higher frequency in MNTX-treated subjects using the subcutaneous formulation compared to the oral formulation except for vomiting and rhinorrhea, which occurred more frequently in oral. The clinical significance of this in regards to OW is unclear, since isolated terms alone do not represent clinical OW. Preferred terms abdominal distention, headache, and blood creatine phosphokinase increased occurred with a higher or equal frequency in oral compared to subcutaneous, but these are not potential OW terms.

Oral MNTX OW Cases (Reviewer Identified)[2]*:* The table below summarizes my findings of the Investigator-identified and DSM-V Criteria identified cases of opioid withdrawal in oral MNTX by individual study and total pooled for the Phase 2 and Phase 3 placebo-controlled studies in which opioid withdrawal cases were reported, using the criteria of DSM-V or investigator-identified cases of opioid withdrawal. As shown, the overall percent of subjects experiencing OW in any individual study was small (≤2%) and the total pooled incidence was 1%. The findings are viewed in the context of the limitations of the studies as previously discussed in reviewer's comments sections of the individual studies.

Table 13. Placebo-Controlled Phase 2 and 3 Studies With Investigator or DSM-V Criteria Identified Opioid Withdrawal Cases (Oral MNTX) – Reviewer Identified

Study (Oral Formulation) DB Duration	**OW Cases Identified**	
	Total N MNTX Number Subjects OW (%)	**Total N Placebo Number Subjects OW (%)**
3201 ((b) (4) tablets) 12 week Double-Blind	N=602 8 (1)	N=201 0
2202 ((b) (4) Capsule) 28 day Double-Blind	N=99 2 (2)	N=29 0
200 ((b) (4) Capsule) 28 day Double-Blind	N=192 1 (<1)	N=44 0
Total Oral PC OIC Pool	N=1057	N=344
Total OW Cases	11 (1)	0

(Reviewer) OIC=Opioid Induced Constipation; (b) (4), (b) (4); N=number; PC=placebo-controlled; MNTX=methylnaltrexone.

Subcutaneous MNTX OW Cases (Reviewer Identified)[2]*:* The table below summarizes the cases of possible opioid withdrawal in double-blind Study 3356 and open-label Study 3358 based upon the original NDA 21-964 submission using the DAAAP reviewer identified criteria previously discussed. DSM criteria analysis was not conducted by the Applicant in studies 3356 and 3358 as submitted in the original NDA 21-964 submission. The table below represents findings from the DAAAP consult which identified possible cases of OW based upon reviewer identified criteria previously discussed. The overall incidence of clinically important OW was ≤2% for individual

[2] Note that the Applicant included summary tables for OW for oral MNTX and subcutaneous MNTX in the ISS, but because they did not provide an explanation for how they derived at their findings, their summary tables were not interpretable.

studies and 1% for all MNTX-treated subjects in the key studies for subcutaneous route of administration of MNTX.

Table 14. Placebo-Controlled and Uncontrolled Phase 3 Studies With Investigator or DSM-V Criteria Identified Opioid Withdrawal Cases (Subcutaneous MNTX)

Study (Duration)	**Possible OW Cases Identified**	
	Total N MNTX Number Subjects OW (%)	**Total N Placebo Number Subjects OW (%)**
3356 (4 week Double-Blind)	N=298 7 (2)	N=162 N/A*
3358 (48 week Open-Label)	N=1034 8 (<1)	No placebo control
Total OW Cases	15 (1)	N/A*

(Reviewer); *Note that in Study 3356, only MNTX-treated subjects were reviewer analyzed for possible OW. Study 3358 was open-label so there was no placebo for comparison.

The findings of possible cases of OW in Studies 3356 and 3358 were considered in light of the limitations of the studies:

- Infrequent assessments of withdrawal may not have captured symptoms during clinically relevant times. Specifically, OOWS/SOWS were obtained at predose, one hour postdose, and not again until days 14 and 28 during the DB period. Although opioid withdrawal may have occurred at any time during treatment, the clinical expectation is that withdrawal would occur early in treatment, likely within the first 7 to 14 days.
- Patients were allowed to increase pain medication throughout study. This may have masked potential changes in pain intensity (PI) scores if the scores were not collected prior to changes in opioid dose.
- The Sponsor provided no defined criteria for mild, moderate or severe rating for OOWS scores.

Reviewer's Comments/Conclusions: Overall, there appears to be a similar incidence of possible investigator and DSM-V criteria OW in oral MNTX compared to subcutaneous. However, because different criteria were used to identify possible OW cases in the oral MNTX than those for the subcutaneous MNTX, the results cannot be directly compared. Further, the limitations of the study designs for both the oral MNTX and subcutaneous MNTX make it challenging to fully identify cases of opioid withdrawal (except those which are Investigator identified). Given the numerous flaws in study design and different criteria used for determination of OW in the oral MNTX and SC, one can really only conclude that opioid withdrawal occurred in some subjects in both the oral and subcutaneous MNTX routes of administration.

VI) Postmarketing Subcutaneous Relistor Opioid Withdrawal Reports

The Applicant provided an overview of Relistor SC postmarketing AEs by SOC received from March 28, 2008 through March 27, 2015 with a cumulative summary of all spontaneous SAEs received through March 27, 2015 (Adverse Events reported in Serious Case Reports). These data in the submission were summarized from all spontaneous sources, including reports received from healthcare professionals, consumers, and competent authorities (worldwide), as well as reports identified from review of the scientific literature. These reports are examined in the setting of worldwide postmarketing exposure estimated at approximately 26,888 patient years. The post marketing experience section of the approved Relistor PI (package insert) states that "cases of opioid withdrawal have been reported," noting that this has been identified during post-approval use of Relistor, and because post-marketing events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The Applicant reports that they conducted a search of the post-marketing safety database for Relistor and identified six SAE case reports describing events of "withdrawal" or "reversal of opiate activity" in the setting of Relistor administration.

VII) Proposed Labeling Discussion

The labeling review is ongoing at the time of this review. With regard to the potential for MNTX to precipitate opioid withdrawal, the proposed label for oral MNTX is generally consistent with approved subcutaneous MNTX which reads, in part, as follows:

- Warnings and Precautions - Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor closely for symptoms of opioid withdrawal.
- Drug Interactions - Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use.
- Use in Specific Populations - Pregnancy: May precipitate opioid withdrawal in a fetus.
- Section 5.3 Opioid Withdrawal: Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using

RELISTOR in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients.

Specific DAAAP recommendations for oral MNTX labeling include the following:

- Section 6.1 Clinical Trials Experience: Adverse reactions in adult patients with opioid-induced constipation and chronic non-cancer pain receiving Relistor tablets are shown in Table 2. *DAAAP recommends the following text be added before the table: AE terms of abdominal pain, diarrhea, anxiety, and hyperhidrosis may reflect symptoms of opioid withdrawal.*

VIII) Reviewer Conclusions:

- There was evidence of opioid withdrawal in a small number of subjects when using oral MNTX. My identification of opioid withdrawal is heavily weighted on investigator and DSM-V criteria identified cases due to the limitations of the other opioid-withdrawal related outcomes (i.e., OOWS, SOWS, pain intensity scores, and isolated preferred terms).

- The following flaws in study design for key Study 3201 limit interpretation of the results:

    - Infrequent assessments of withdrawal may not have captured symptoms during clinically relevant times. Specifically, OOWS/SOWS were obtained at predose, one hour postdose, and not again until day 14 during the double-blind period. Although opioid withdrawal may have occurred at any time during treatment, the clinical expectation is that withdrawal would occur early in treatment, likely with the first seven to 14 days.

    - Patients were allowed to increase pain medication throughout the study. This may have masked potential changes in pain intensity (PI) scores if the scores were not collected prior to changes in opioid dose.

    - The Sponsor provided no defined criteria for mild, moderate, or severe rating for the OOWS or SOWS scores.

- Opioid withdrawal in methadone-maintained subjects revealed that across all studies conducted in methadone-maintained subjects, 15 subjects (12%) were identified as experiencing opioid withdrawal (OW). Of the 15 subjects, 12 experienced OW after the subcutaneous route compared to only three who received an oral formulation of MNTX. No cases of OW were identified in

placebo. This suggests that in methadone-maintained subjects, the subcutaneous MNTX has a higher risk of OW than oral. The highest incidence of OW was in Study 105. The generalizability of the findings from Study 105, however, are limited due to the small sample size (i.e., 24 MNTX subjects) with no placebo for comparison, and this patient population (i.e., methadone-maintained) may differ from patients taking opioids for chronic non-cancer pain.

- Overall, there appears to be a similar incidence of possible OW in oral MNTX compared to subcutaneous. However, because different reviewer criteria were used to identify possible OW cases in the oral MNTX than those for the subcutaneous MNTX, the results cannot be directly compared. The Applicant is not seeking comparative labeling claims regarding opioid withdrawal.

IX) DAAAP's Responses to DGIEP Questions

For Study 3201:

1) Did the Applicant sufficiently assess the impact of methylnaltrexone bromide on opioid withdrawal?

DAAAP Response: No, the Applicant did not sufficiently assess the impact of methylnaltrexone bromide on opioid withdrawal in Study 3201 due to flaws in study design. It should be noted that for sNDA 21964 efficacy supplement for subcutaneous MNTX in OIC patients, DAAAP was consulted and similarly found that Studies 3356 and 3358 were not adequately designed to assess opioid withdrawal. However, after the Advisory Committee, the Agency determined that although Studies 3356 and 3358 were not adequately designed to capture opioid withdrawal cases, based upon investigator-identified and DSM criteria- identified cases, we concluded that there were cases of opioid withdrawal (b) (4) **The scenario for this NDA is similar to that for sNDA 21964 in that the study design flaws for Study 3201** (b) (4) **, but from a safety perspective, using both investigator and DSM criteria, cases of opioid withdrawal were identified to allow for inclusion in and support of the proposed label.**

2) Is there evidence of opioid withdrawal in methylnaltrexone bromide compared to placebo?

DAAAP Response: Given the totality of opioid withdrawal assessments for the oral formulation across multiple studies, and using the criteria of Investigator or DSM-V identified cases of opioid withdrawal in these studies, the Sponsor has

provided data to support the conclusion that some cases of opioid withdrawal occurred in the subjects treated with oral MNTX compared to no cases in placebo-treated subjects, using the same criteria.

3) Other DAAAP Comments:

- **The following advice was given to the Applicant at a Pre-NDA meeting in 2012, "You should not only record daily opioid doses administered by subjects but also capture any changes in doses that occur throughout the 12-week double blind treatment period. In addition, you should assess pain daily using a visual analogue scale (VAS) and analyze for any correlation between the changes in opioids and pain ratings." The Applicant did not follow that advice for unknown reasons.**

Appendix A . Opioid withdrawal Assessment Scales

Table 1. OOWS (Original Handlesman) and Used in Key Study 3201

Instructions: Read each item below carefully and place an "X" in either the PRESENT or the NOT PRESENT column. Please answer each item.

OBSERVATIONS:	NOT PRESENT (0)	PRESENT (1)	
1. Yawning (One or more = present)	☐	☐	
2. Rhinorrhea (Three or more = present)	☐	☐	
3. Piloerection (Gooseflesh – observe patient's arm)	☐	☐	
4. Perspiration	☐	☐	
5. Lacrimation	☐	☐	
6. Mydriasis (Pupil Dilation)	☐	☐	
7. Tremors (Hands)	☐	☐	
8. Hot & cold flashes (Shivering or huddling for warmth)	☐	☐	
9. Restlessness (Frequent shifts of position)	☐	☐	
10. Vomiting	☐	☐	
11. Muscle twitches	☐	☐	
12. Abdominal cramps (Holding stomach)	☐	☐	
13. Anxiety* (M-mild; MD=moderate; S=severe)	☐	☐	Circle One if present M - MD - S
TOTAL	☐		

**Mild*: observable manifestations – foot shaking, fidgeting, finger-tapping.
Moderate to severe: agitations, unable to sit, trembling, panicky; complains of difficulty in breathing, choking sensations, palpitation.

(Protocol, p. 81)

Table 2. Original SOWS (Handlseman)

1. I feel anxious
2. I feel like yawning
3. I'm perspiring
4. My eyes are tearing
5. My nose is running
6. I have goose flesh
7. I am shaking
8. I have hot flashes
9. I have cold flashes
10. My bones and muscles ache
11. I feel restless
12. I feel nauseous
13. I feel like vomiting
14. My muscles twitch
15. I have cramps in my stomach
16. I feel like shooting up now

Table 3. Applicant's Modified SOWS Used in Key Study 3201

Instructions: Answer the following statements as accurately as you can. Rate the way you have been feeling the PAST 24 HOURS according to the scale below by placing an "X" in the appropriate box.

Please check the box, which is the most appropriate for how you have been feeling.	Not At All (0)	A Little (1)	Moderately (2)	Quite A Bit (3)	Extremely (4)	
1. I have felt anxious.	☐	☐	☐	☐	☐	
2. I have been yawning.	☐	☐	☐	☐	☐	
3. I have been perspiring.	☐	☐	☐	☐	☐	
4. My eyes have been tearing.	☐	☐	☐	☐	☐	
5. My nose has been running.	☐	☐	☐	☐	☐	
6. I have had gooseflesh.	☐	☐	☐	☐	☐	
7. I have been shaking.	☐	☐	☐	☐	☐	
8. I have had hot flashes.	☐	☐	☐	☐	☐	
9. I have had cold flashes.	☐	☐	☐	☐	☐	
10. My bones and muscles have been aching.	☐	☐	☐	☐	☐	
11. I have been feeling restless.	☐	☐	☐	☐	☐	
12. I have been feeling nauseous.	☐	☐	☐	☐	☐	
13. I have felt like vomiting.	☐	☐	☐	☐	☐	
14. My muscles have been twitching.	☐	☐	☐	☐	☐	
15. I have had cramps in my stomach.	☐	☐	☐	☐	☐	
16. I have felt like taking more pain medication.	☐	☐	☐	☐	☐	
17. I have had trouble sleeping.	☐	☐	☐	☐	☐	
18. My appetite has been poor.	☐	☐	☐	☐	☐	
19. I have had diarrhea.	☐	☐	☐	☐	☐	
TOTAL SCORES	☐	☐	☐	☐	☐	☐

(Protocol, p. 82-83)

Appendix B: Clinician Opioid Withdrawal Scale (COWS)

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactiv Drugs*. 35(2). 253–9.

Severity Scale: 5-12=mild**; 13-24**=moderate; **25-36=**moderately severe; **More than 36=**severe withdrawal

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/s/

ELIZABETH M KILGORE
03/21/2016

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Division of Pediatric and Maternal Health Memorandum

Date: March 14, 2016 **Date Consulted:** June 22, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Relistor (methylnaltrexone bromide) tablets, 150mg

Indication: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

NDA: 208271

Applicant: Salix Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- DPMH consult request dated June 22, 2015, DARRTS Reference ID 3782498
- Applicant's submitted background package for NDA 208271, Relistor (methylnaltrexone bromide) tablets
- DPMH Review: Relistor (methylnaltrexone bromide), NDA 21964. Miriam Dinatale, D.O. September 12, 2014. DARRTS Reference ID 3625769.

CONSULT QUESTION

"DGIEP requests DPMH assistance with review of the label for this application."

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on June 22, 2015, to review the Pregnancy and Lactation subsections of the Relistor labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

REGULATORY HISTORY

On June 19, 2015, Salix Pharmaceuticals, Inc., submitted a 505(b)(1) New Drug Application (NDA) for Relistor (methylnaltrexone bromide) tablets (NDA 208271), a newly proposed oral formulation, with the same proposed indication (treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain) as the currently marketed formulation of Relistor, NDA 21964. Relistor (methylnaltrexone bromide) Subcutaneous Injection, NDA 21964, the reference listed drug, was initially approved by the FDA on April 24, 2008, for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. An efficacy supplement for Relistor subcutaneous injection (NDA 21964/s-010), for the treatment of OIC in adult patients with chronic non-cancer pain, was approved on September 29, 2014. The proposed Relistor labeling provides prescribing information for both the injection and the new tablet formulation.

BACKGROUND

Methylnaltrexone and Drug Characteristics

Relistor (methylnaltrexone bromide) is a selective μ-opioid receptor antagonist and a quaternary derivative of the opioid antagonist, naltrexone. The applicant hypothesized that Relistor's access to the blood brain barrier would be limited, allowing methylnaltrexone bromide to function peripherally in the small and large intestine to decrease the constipating effects of opioids. However, there were case reports of opioid withdrawal symptoms (1.3 per 100 patients) in the Relistor Phase 3 clinical trial for OIC in patients with non-cancer pain.[1] Also, patients with disruptions in the blood-brain barrier, who may have had a higher risk of opioid withdrawal with methylnaltrexone use, were excluded in the Phase 3 clinical trials.

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories

[1] See current approved Relistor labeling,

[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

(A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

DISCUSSION

Methylnaltrexone and Nonclinical Studies

The applicant's proposed methylnaltrexone labeling includes data from animal reproduction studies that were conducted for the initial approval of methylnaltrexone subcutaneous injection in 2008. In these animal reproduction studies, there was no evidence of embryo-fetotoxicity observed with the administration of intravenous methylnaltrexone during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the maximum recommended human dose (MRHD) of 12 mg per day. The applicant is relying on previous nonclinical findings and did not submit nonclinical studies with this NDA. The reader is referred to previous DGIEP Nonclinical reviews of Relistor Subcutaneous Injection by Tamal Chakraborti, Ph.D.[4,5] and the current review for Relistor Tablets by Sushanta Chakder, Ph.D. for a comprehensive review of the animal reproduction studies.

Methylnaltrexone and Pregnancy

A search of published literature was performed by the applicant and DPMH to update the Pregnancy section of labeling for this application. No studies or data with methylnaltrexone use in pregnant women were found in PubMed or Embase. However, there were four pregnancies that occurred in a phase 3 open-label safety study (Study 3358). There was no investigator examination of the infants, and the status of infant health was reported by the mothers. These four pregnancy case reports are summarized below. Two of the pregnancy reports occurred in one subject.

- A 35 year-old Black female with a history of OIC, osteoarthritis and anxiety disorder became pregnant while taking methylnaltrexone. The subject was also taking methadone and Xanax. The subject was discontinued from the study on December 10, 1999 (study day 169) after diagnosis of pregnancy. The pregnancy was complicated by placental abruption with a premature female infant born at 28 weeks gestation and weighing two pounds. The applicant's only follow-up information is based on a report from the infant's mother, who reported that the infant was well. No additional follow-up information was provided.

- A 29 year-old White female with OIC, back pain, depression and anxiety became pregnant while taking methylnaltrexone. The subject was also taking hydrocodone, fluoxetine and lorazepam. The subject had a spontaneous abortion on August 24, 2009 (study day 88) and was continued in the trial. She was discontinued from the

[3] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[4] Nonclinical Review: Relistor (methylnaltrexone) Subcutaneous Injection, NDA 21964/S-10. Tamal Chakraborti, Ph.D. September 4, 2014. DARRTS Reference ID 3621716.
[5] Nonclinical Review: Relistor (methylnaltrexone) Subcutaneous Injection, NDA 21964. Tamal Chakraborti, Ph.D. March 30, 2007.

study on January 8, 2010 (study day 225) after diagnosis of her second pregnancy. The subject delivered a premature male infant weighing 4 pounds, 2.7 ounces at 34 weeks gestation. The applicant's only follow-up information is based on a report from the infant's mother, who reported that the infant was healthy and that both she and the infant had an uncomplicated postpartum recovery.

- A 32 year-old White female with OIC, migraines, seasonal allergies, asthma, and GERD became pregnant while taking methylnaltrexone. The patient was also taking Tri-Sprintec, hydroxyzine, Prevacid, Advair, promethazine, cyclobenzaprine, and oxycodone. The subject was discontinued from the study on August 12, 2009 (study day 57) after diagnosis of pregnancy. The subject delivered a healthy male infant weighing 5 pounds 5 ounces at 36 weeks gestation[6]. The applicant's only follow-up information is based on a report from the infant's mother, who reported there were no complications during labor or delivery.

Summary
Given the limited number of cases reported as well as the use of many concomitant medications in these pregnancies, it is difficult to draw any conclusions regarding the use of Relistor during pregnancy. In addition, the applicant did not examine the infants of women who had been exposed to Relistor during pregnancy; therefore, the only information about the infant is based on reports from the infants' mother, and do not appear to have been confirmed by a health care provider or investigator.

However, since most drugs cross the placenta, and signs and symptoms of withdrawal occurred in adult subjects in clinical trials, Relistor has the potential to precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier, as is the case with other opioid antagonists. In a review article by John McCarthy[7], the author noted that fetal opioid withdrawal is a potentially fatal syndrome and that if the mother is having opioid withdrawal, then the fetus is most likely having opioid withdrawal as well. The fetus is at risk for seizures, hyperactivity, and catecholamine excess. Fetal oxygen consumption is increased, and the infant is at risk for asphyxia. There are two additional studies that describe fetal opioid withdrawal and are referenced by McCarthy.

- There is a case study (Wong, *et al*.) using Doppler analysis of the umbilical artery that demonstrated absent end diastolic flow during heroin withdrawal.[8]
- There was a case report (Zuspan, *et al*.) that reported on the 1973 FDA mandate that required pregnant woman taking methadone to undergo a 21-day withdrawal. The authors documented one fetal death that occurred during withdrawal that was preceded by excessive intrauterine movements. [9]

[6] Normal gestational weight for an infant born at 36 weeks gestation is >4lb 13 oz.
[7] McCarthy, John. Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: Can we assure the safety of the fetus? The Journal of Maternal-Fetal and Neonatal Medicine. 2-12: 25 (2): 109-112.
[8] Wong WM, Lao TT. Abnormal umbilical artery flow velocity waveform–a sign of fetal narcotic withdrawal? Aust N Z J Obstet Gynaecol 1997;37:358–359.
[9] Zuspan FP, Gumpel JA, Mejia-Zelaya A, Madden J, Davis R. Fetal stress from methadone withdrawal. Am J Obstet Gynecol1975;122:43–46.

In the DPMH review of another opioid receptor antagonist, the reviewer cites an article about the effect of naloxone on fetal behavior near term and noted the following:

> "In the naloxone group, the number of fetal body movements and fetal breathing movement increased over time but especially during the first hour. Additionally, increases were seen in the naloxone group in the number, duration and amplitude of fetal heart rate accelerations and in the active sleep and active awake states. The authors concluded these differences to be because of the reversal of the effects of fetal endorphins."

The reader is referred to the DPMH review of Movantik (naloxegol) by Carrie Ceresa, PharmD, MPH for further details.[10]

Methylnaltrexone and Lactation

A search of published literature for available human lactation data was performed to update the lactation section of labeling for this application. No studies or data with methylnaltrexone use in lactating women were found in the Drugs and Lactation Database (LactMed),[11] PubMed, or Embase. Although there are no data on the transfer of methylnaltrexone in human milk, methylnaltrexone has caused gastrointestinal perforation, severe or persistent diarrhea and opioid withdrawal in clinical trials with adult patients.

In an animal lactation study, methylnaltrexone bromide was present in rat milk following subcutaneous administration of radiolabeled methylnaltrexone (^{3}H-MNTX) on postpartum day 10. The Cmax value in the maternal plasma (2.08 micrograms equivalents /gram) was observed at 0.5 hours after dosing and decreased to 0.0528 microgram equivalents /gram at 8 hours. The concentrations of radioactivity in rat milk increased from 0.202 microgram equivalents/gram at 0.5 hours to 1.25 microgram equivalents/gram at 8 hours. The milk to maternal plasma concentration ratios at 0.5 and 8 hours after dosing were 0.1 and 24, respectively. These data indicate that ^{3}H-MNTX is present in rat milk. The reader is referred to the previous DGIEP Nonclinical review of Relistor Subcutaneous Injection by Tamal Chakraborti, Ph.D. for a comprehensive review of the animal lactation study.[12]

Summary

Methylnaltrexone is present in rat milk at up to 24-fold higher concentrations in maternal milk than plasma. Drug presence and accumulation in breast milk is species specific. Although methylnaltrexone has characteristics, such as molecular weight (436.36 Daltons), a short half-life, and low protein-binding (11-15%), that suggest the drug is transferred into breast milk, there are no data with methylnaltrexone use in lactating women and limited

[10] DPMH review of Movantik (naloxegol oxalate) tablets. NDA 204760. May 14, 2014. Carrie Ceresa, PharmD, MPH. DARRTS Reference ID 3506381.

[11] 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.

[12] Nonclinical Review: Relistor (methylnaltrexone) Subcutaneous Injection, NDA 21964. Tamal Chakraborti, Ph.D. March 30, 2007.

understanding regarding whether or not methylnaltrexone would concentrate in breast milk.[13]

DPMH agrees with the applicant and recommends against breastfeeding with maternal use of Relistor due to the potential for opioid withdrawal in a breastfed infant. Furthermore, breastfeeding is not recommended with chronic opioid use, and since female patients taking Relistor are likely being administered opioid medication chronically, these female patients should not be breastfeeding.

Methylnaltrexone and Females and Males of Reproductive Potential
DPMH conducted a PubMed and Embase search for available published literature on methylnaltrexone and its effects on fertility, and no studies were found. In animal fertility studies, subcutaneous methylnaltrexone given to male and female rats at doses 122 times the MRHD did not have any adverse effects on fertility. Given the lack of information in published literature regarding methylnaltrexone and fertility and reassuring animal fertility studies, subsection 8.3, Females and Males of Reproductive Potential, will not be included in labeling.

CONCLUSIONS
The proposed Relistor labeling, addressing both the injection and the new tablet formulation, has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with Relistor use in pregnant or lactating women. DPMH has the following recommendations for Relistor labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Relistor labeling was structured in the PLLR format to include the "Risk Summary" and "Data" subsections.[14]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Relistor labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections.[15]
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" subsection of Relistor labeling was formatted to include a review of information that had been presented in sections 8.1 and 8.2.

RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2 and 17 in Relistor labeling for compliance with the PLLR (see below). See Appendix A for the applicant's proposed Relistor labeling. DPMH refers to the final NDA action for final labeling.

[13] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.
[14] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[15] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

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/s/

MIRIAM C DINATALE
03/14/2016

LYNNE P YAO
03/16/2016

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 16, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 208271
Product Name and Strength:	Relistor (methylnaltrexone bromide) Tablets
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Salix Pharmaceuticals, Inc.
Submission Date:	June 19, 2015
OSE RCM #:	2015-1411
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review is in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) with regard to Relistor (methylnaltrexone bromide) tablets (NDA 208271). This new NDA proposes a new dosage form (tablets) for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. DGIEP requested that DMEPA review the proposed Prescribing Information, container labels, and carton labeling for any areas of vulnerability that may lead to medication errors.

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
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Salix Pharmaceuticals, Inc. submitted a new NDA to obtain marketing approval of Relistor 150 mg tablets. Relistor is currently marketed in 8 mg/0.4 mL solution for subcutaneous injection in prefilled syringes and 12 mg/0.6 mL solution for subcutaneous injection in single-dose vials and prefilled syringes (NDA 21964). The Applicant is proposing a new oral tablet dosage form of Relistor (methylnaltrexone bromide), with a dose of 450 mg once daily as an effective alternative to the currently approved subcutaneous administration for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain. Additionally, the Applicant proposes to market the proposed oral dosage form under the same proprietary name as the currently available Relistor (methylnaltrexone bromide) solution for subcutaneous injection.

DMEPA evaluated the introduction of this new dosage form of tablets and reviewed the proposed labels and labeling to determine whether there are any vulnerabilities that may lead to medication errors. DMEPA finds the introduction of the proposed oral dosage form acceptable from a medication error perspective. We found the proposed prescribing information, carton labeling and container labels are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The prescribing information, carton labeling and container labels are acceptable from a medication error perspective and we have no further comments at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Relistor label and labeling submitted by Salix Pharmaceuticals, Inc. submitted on June 19, 2015.

Table 2. Relevant Product Information for Relistor		
Product	Relistor (NDA 21964)	Relistor (NDA 208271)
Initial Approval Date	April 24, 2008	Currently under review.
Active Ingredient	methylnaltrexone bromide	
Indication	Both tablets and injection are indicated for the treatment of opioid induced constipation (OIC) in adults with chronic non-cancer pain.	
	Injection is indicated for the treatment of OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.	
Route of Administration	subcutaneous injection	oral
Dosage Form	injection	tablets
Strengths	• 8 mg/0.4 mL in a single-dose prefilled syringe • 12 mg/0.6 mL in a single-dose prefilled syringe and single-dose vial	150 mg
Dose and Frequency	**Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain:** • 12 mg administered subcutaneously once daily. • Patients with severe renal impairment (CrCl <30 ml/min as estimated by Cockcroft-Gault): 6 mg administered subcutaneously once daily **Opioid-Induced Constipation in Adult Patients with Advanced Illness:** • One dose administered subcutaneously every other day, as needed. See table	**Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain:** • 450 mg taken orally once daily in the morning. • (b) (4)

below for recommended weight-based dose and corresponding injection volume.

Table 1: Weight-Based Dosing of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC and Advanced Illness

Weight of Adult Patient	Subcutaneous Dose	Injection Volume
Less than 38 kg	0.15 mg/kg	**See below***
38 kg to less than 62 kg	8 mg	**0.4 mL**
62 kg to 114 kg	12 mg	**0.6 mL**
More than 114 kg	0.15 mg/kg	**See below***

*Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL

- Patients with severe renal impairment (CrCl <30 ml/min as estimated by Cockcroft-Gault): One dose administered subcutaneously every other day, as needed. See table below for recommended weight-based dose and corresponding injection volume.

Table 2: Weight-Based Dosing in Severe Renal Impairment of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC and Advanced Illness

Weight of Adult Patient	Subcutaneous Dose	Injection Volume

mg once daily in the morning.

- Patients with moderate or severe hepatic impairment (Child-Pugh Class B or C): 150 mg once daily in the morning.

<table>
<tr><td></td><td>
<table>
<tr><td>Less than 38 kg</td><td>0.075 mg/kg</td><td>See below*</td></tr>
<tr><td>38 kg to less than 62 kg</td><td>4 mg</td><td>0.2 mL</td></tr>
<tr><td>62 kg to 114 kg</td><td>6 mg</td><td>0.3 mL</td></tr>
<tr><td>More than 114 kg</td><td>0.075 mg/kg</td><td>See below*</td></tr>
</table>
*Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL.
</td><td></td></tr>
<tr><td>How Supplied</td><td>8 mg/0.4 mL:
• 7 prefilled syringes per carton
12 mg/0.6 mL:
• 1 vial per carton
• 1 pre-filled syringe per carton
• 7 prefilled syringes per carton</td><td>60 and 90 count bottles</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Protect from light.</td><td>Store at up to 25°C (77°F); excursions permitted to 15°C– to 30°C (59°F– to 86°F) [see USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Relistor label and labeling submitted by Salix Pharmaceuticals, Inc. on June 19, 2015.

Prescribing Information
Container labels and carton Labeling

G.2 Label and Labeling Images

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

Carton Labeling:

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/s/

SHERLY ABRAHAM
02/16/2016

MISHALE P MISTRY
02/17/2016

LUBNA A MERCHANT
02/17/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Medical Team Leader
DPMH

NDA Number: 208271

Sponsor: Salix Pharmaceuticals

Drug: Relistor (methylnaltrexone bromide)

Indication: Treatment of:

- Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
- OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

Dosage form and route of administration: 150 mg tablets for oral (PO) administration

Proposed Adult regimen: 150 to 450 mg PO once daily

Division Consult Request: The Division of Gastroenterology and Inborn Error Products (DGIEP) requested assistance from both the Pediatric Team and the Maternal Health Team for labeling of this new NDA. However, DGIEP plans to approve the product in adults only because no pediatric data has been submitted and the sponsor has requested a full waiver of pediatric studies.

Therefore, as agreed upon per discussions with DGIEP, this consult will focus primarily on the sponsor's request for waiver of studies under Pediatric Research Equity Act (PREA).

Materials Reviewed

Relistor (NDA 208271)
Consult Request
Request for Waiver of Pediatric Studies (0 through 17 years)

Relistor (NDA 21964)
PMHS (now DPMH) Consult: J. Best; March 11, 2010; J. Best; March 27, 2012
Pediatric Inadequate PPSR Inadequate Letter: D. Griebel, April 8, 2010
Ethics Consult: R. Nelson, August 26, 2010

Naloxegol (IND 78781)
PMHS Consult: E. Hausman, April 4, 2014
PMHS Consult: J. Best; March 26, 2013

Naldemedine (IND 107475)
DPMH Consult: E. Hausman, September 18, 2015

Background

Relistor (methylnaltrexone bromide; tablets and subcutaneous injection) is a peripheral mu-opioid receptor antagonist (PMORA) thought to have predominant or exclusive effects outside the central nervous system (CNS). The main site of action may be the gastrointestinal tract, allowing for decrease of the constipating effects of opioids without affecting opioid-mediated analgesia in the CNS. The newly proposed PO formulation (NDA 208,271) proposes the same indication as the currently marketed formulation (NDA 21964, approved by FDA on April 24, 2008). There is no pediatric data submitted for a labeling indication for this application or for the previously marketed formulation.

Proposed Pediatric Labeling

"Safety and effectiveness of RELISTOR have not been established in pediatric patients.

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing were observed, and the juvenile rats were found to be more sensitive to the adverse effects of methylnaltrexone bromide when compared to adult animals. Juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks had a toxicity profile similar to adult dogs *[see Nonclinical Toxicology (13.2)]*."

Reviewer comment: The above text is identical to the currently marketed injection product. At the labeling meeting of February 1, 2015, DPMH, Toxicology, and DGEIP agreed that the description of juvenile toxicity data in section 8.4, combined with toxicology data in section 13.2, adequately characterizes animal toxicity data associated with this product. DPMH suggests placing the header "Juvenile Toxicity" before the second paragraph beginning "In juvenile rats…"

Request for Full Waiver of Pediatric Studies

The application includes plan for a full waiver of studies in pediatric patients 0 through 17 years due to the low number of pediatric patients with chronic opioid use (and therefore few patients with OIC associated with chronic opioid use).

A full waiver is consistent with other recent pediatric plans for treatment of OIC in patients with chronic non-cancer pain including naloxegol (Approval Letter, NDA 204,760, September 16, 2014) and advice given in a recent DPMH review for naldemedine (another PMORA under development for treatment of OIC-associated constipation; DPMH review, IND 107475, September 18, 2015).

Prior discussions surrounding two similar products, described in the prior DPMH consult review referenced above and the naloxegol Approval Letter, highlight three key factors whereby the Pediatric Review Committee (PeRC) and DGIEP determined that studies under the Pediatric Research Equity Act (PREA) were deemed impossible or highly impracticable and thus, would support a full waiver of pediatric studies. First, the methylnaltrexone pediatric program was ultimately suspended due to difficulty enrolling pediatric patients. Second, at a PeRC meeting in February 2012, PeRC and DGIEP agreed that at least 4 weeks of round-the-clock opioid/naltrexone exposure would be required to develop OIC and assess treatment effect. Third, PeRC and DGIEP concluded that a review of literature performed by an FDA working group failed to identify a pediatric population that would likely require opioid use for at least 4 weeks (i.e., too few patients or too geographically dispersed to study).

OxyContin (NDA 22272) was recently approved (August 13, 2015) for pediatric patients requiring round-the-clock (RTC), long-term opioid treatment (at least 2 weeks in pediatric studies) and for whom alternative treatment options are inadequate (specifically, patients tolerate at least 20 mg of oxycodone or its equivalent). This does not contravene the rationale for deferring pediatric studies under PREA since the PeRC determined that at least 4 weeks of round the clock exposure would be required to render a population likely to develop OIC.

Conclusion

The above advice was provided to DGIEP at the internal meeting of January 20, 2016. DPMH continues to provide assistance with preparation for presentation to the Pediatric Review Committee (PeRC). The reader is directed to the PeRC meeting minutes (pending) and the final negotiated labeling (pending) for additional details.

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/s/

ETHAN D HAUSMAN
02/02/2016

HARI C SACHS
02/02/2016
I agree with these recommendations.

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: January 20, 2016

TO: James Carr, Regulatory Project Manager
Dina Zand, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 0208271

APPLICANT: Salix Pharmaceuticals, Inc.
DRUG: Relistor®
NME: No
THERAPEUTIC CLASSIFICATION: Standard

INDICATION: For the treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain"

CONSULTATION REQUEST DATE: August 20, 2015
INSPECTION SUMMARY GOAL DATE: February 1, 2016
DIVISION ACTION GOAL DATE: April 19, 2016
PDUFA DATE: April 19, 2016

I. BACKGROUND:

Salix Pharmaceuticals submitted NDA 208271 for the indication of treatment of opioid-induced constipation in adults with chronic non-cancer pain. Despite analgesic efficacy, opioid use may be complicated by a number of dose-limiting adverse events (AE), the most common of which is opioid-induced constipation (OIC). OIC is characterized by infrequent, difficult, or incomplete bowel movements, and is mediated primarily by the direct stimulation of μ-opioid receptors in the gastrointestinal (GI) tract by prescribed opioids, leading to a decrease in GI motility and ultimately constipation.

Relistor® (Methylnaltrexone) was approved by FDA in 2008 as a subcutaneous (SC) injection for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Although the SC administration is effective and well tolerated, an oral MNTX (OM) tablet formulation was developed with the intention that there would be better patient acceptance.

The review division requested inspection of the clinical trial Protocol MNTX3201 entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Subjects with Chronic, Non-Malignant Pain"

Sites were chosen for inspection on the basis of high enrollment, numbers of INDs in the OSI database, and previous inspectional history.

II. RESULTS (by Site):

Type of Inspected Entity, Name, and Address	Protocol #/ Site #/ # of Subjects	Inspection Date	Classification*
CI: Atoya Adams, MD, MBA 2121 E. Flamingo Road, Suite 107 Las Vegas, NV 89119	MNTX3201/ Site 001/ 29	October 19 to 22, 2015	NAI
CI: V. Jerome Mirkil, MD 2110 E. Flamingo Road, Suite 119 Las Vegas, NV 89119-5190	MNTX3201/ Site 025/ 28	October 12 to 19, 2015	VAI
CI: Steve Choi, MD Hometown Urgent Care and Research 1010 Woodman Drive Dayton, OH 45432	MNTX3201/Site 039/ 25	October 19 to 26, 2015	Pending NAI
CI: Echo Chiu, MD Lotus Clinical Research, LLC 100 W. California Blvd, Pasadena, CA 91105	MNTX3201/ Site 062/ 39	November 17 to 23, and November 30 to December 1, 2015	Pending NAI
CI: Robert Rosenberg, MD 6707 N. 19th Ave., Suite 201 Phoenix, AZ 85015	MNTX3201/ Site 143/ 29	October 13 to 16, 2015	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Atoya Adams, M.D., MBA**
   2121 E. Flamingo Road, Suite 107, Las Vegas, NV 89119

a. **What was inspected:** At this site for Protocol MNTX3201, 34 subjects were screened, 29 subjects were enrolled into the study, and 23 subjects completed the study. The source documents were reviewed for all six subjects who discounted early, protocol deviations were checked for ten subjects, adverse event listings were verified for five subjects and test article verification was conducted for four subjects. IVRS diary data at the site were compared with the line listings submitted in the NDA for the primary endpoints for five subjects.
b. **General Observations/Commentary:** There were no discrepancies noted between the subject diary entries and the line listings. There was no evidence of

under-reporting of protocol deviations.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. V. Jerome Mirkil, MD
2110 E. Flamingo Road, Las Vegas, NV 89119-5190

a. **What was inspected:** At this site, for Protocol MNTX3201, 45 subjects were screened, 28 subjects were enrolled, and 24 subjects completed the study. The IVRS diary data were reviewed for 11 subjects and compared to the line listings provided in the background material. The source records for 11 subjects who were screen failures or discontinued subjects were reviewed. Source records for five subjects were reviewed for adverse events, and source records for four subjects were reviewed for concomitant medications.

b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data listings submitted by the sponsor to the NDA. A Form FDA 483 was issued for failing to follow the protocol. Specifically, Subject 023-030, randomized to placebo, should have been excluded because of use of rescue laxative within the 72 hour period after a bowel movement (exclusion criterion at baseline visit #2). This violation was noted in the NDA line listings as a protocol violation. The clinical investigator acknowledged the observation and adequately responded to the inspection findings in a letter dated October 20, 2015.

c. **Assessment of data integrity:** The violation noted above appears isolated and does not impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Steve Choi, MD
Hometown Urgent Care and Research, 1010 Woodman Drive, Dayton, OH 45432

a. **What was inspected:** At this site for Protocol MNTX3201, a total of 50 subjects were screened, 25 subjects were enrolled, and 20 subjects completed the study. The records for ten enrolled subjects were reviewed. The records were compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.

b. **General Observations/Commentary:** Records were found to be adequate. The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued because incorrect dosing instructions were given to certain subjects. Specifically, concerning Study 202, for medication dispensed on Day 29 for four subjects, the subjects

were instructed to take one capsule three hours after the last meal whereas the protocol instructions were to take one capsule 30 minutes before breakfast. These incorrect instructions were also provided to one subject on Days 0 and 57 and to another subject on Day 57 only.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appears acceptable in support of the respective indication.

Note: Observations above for this Clinical Investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

4. Echo Chiu, MD
Lotus Clinical Research, LLC, 100 W. California Blvd, Pasadena, CA 91105

a. **What was inspected:** For Protocol MNTX3201, 97 subjects were screened, 39 subjects were enrolled, and 33 subjects completed the study. The records for 20 enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.

b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. No violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

Note: Observations above for this Clinical Investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

5. Robert Rosenberg, MD
6707 N. 19th Ave., Suite 201, Phoenix, AZ 85015

a. **What was inspected:** For Protocol MNTX3201, 64 subjects were screened, a total of 29 subjects were enrolled, and 19 subjects completed the study. The records for 11 enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.

b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites were inspected for this application. Two of the reviews are preliminary and based on e-mail communications. Four of the inspections have a final or preliminary classification of NAI. For Dr. Mirkil's site, the only site with the classification of VAI, the violation is considered minor and does not affect data reliability.

The study appears to have been conducted adequately, and the data generated by the study are acceptable in support of the respective indication. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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

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

/s/

SUSAN LEIBENHAUT
01/21/2016

SUSAN D THOMPSON
01/21/2016

KASSA AYALEW
01/21/2016

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 # 208271 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☒ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: RELISTOR Established/Proper Name: methynaltrexone bromide tablets Dosage Form: oral Strengths: 150mg		
Applicant: Salix Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: June 19, 2015 Date of Receipt: June 19, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: April 19, 2016	Action Goal Date (if different):	
Filing Date: August 18, 2015	Date of Filing Meeting: August 3, 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): **Treatment of Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain**		
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.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
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 ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ 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 (FDCA Section 505B) ☐ 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): 67452	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA 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 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.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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 been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar 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 *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ 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
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☒ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• 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 bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same 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 another listed drug product containing the same active moiety, 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***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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 the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

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 (3397/3792), 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."***	☒	☐		

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, <u>both</u> 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**
<u>For NMEs:</u> 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:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

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

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	*Submitted through IR following NDA submission on 8.14.15*
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	*See comment above no agreed upon iPSP at time of NDA submission*
BPCA: 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 format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

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

[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.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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/PLLR 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 in OPQ (OBP or ONDP)?	☒	☐	☐	
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.***	☐	☐	☐	

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

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

If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging 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) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	DAAP 8/1/15 DPMH 6/22/15
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 3.7.12 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** 6.24.05 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		No agreement

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 3, 2015

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jay Carr	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Laurie Muldowney		Y
Division Director/Deputy	Donna Griebel/Andrew Mulberg		Y
Office Director/Deputy			
Clinical	Reviewer:	Dina Zand	Y
	TL:	Laurie Muldowney	Y
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:	Dilara Japper	Y
	TL:	Sue-Chih Lee	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Justin Earp (Nitin Mehrotra TL)	N
• Biostatistics	Reviewer:	Shahla Farr/Andrejus Parfionovas	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sushanta Chakder	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Danuta Gromek-Woods	Y
	RBPM:	Heather Strandberg	Y
• Drug Substance	Reviewer:	Sam Bain	Y
• Drug Product	Reviewer:	Sarah Ibrahim	Y
• Process	Reviewer:	Bo Jiang	Y
• Microbiology	Reviewer:	Bi Jiang	Y
• Facility	Reviewer:	Marisa Heayn	Y
• Biopharmaceutics	Reviewer:	Vidula Kolhatkar	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	Y
	TL:	Marcia Britt Williams	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Meeta Patel	Y
	TL:	Adewale Adeleye	Y
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Sheryl Abraham	Y
	TL:	Kendra Worthy	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Thompson	Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• PMH	Reviewer:	peds-Ethan Hausman mat-Miriam Dinatale	Y
	TL:	peds-Hari Sachs mat-Tamara Johnson	Y
• DAAP	Reviewer:	Liz Kilgore	Y
	TL:	Joshua Lloyd	Y
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ 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:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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:
• 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
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
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**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **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: Donna Griebel **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **11/30/15** **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. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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/s/

JAMES B CARR
09/02/2015

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

DATE: 9/2/2015

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 208271

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PPD Development	7551 Metro Center Drive, Suite 200, Austin, TX

Nicola M. Nicol -S

Digitally signed by Nicola M. Nicol -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola M. Nicol -S
Date: 2015.09.02 12:12:38 -04'00'

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/s/

NICOLA M FENTY-STEWART
09/02/2015