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RESEARCH**

APPLICATION NUMBER:

208271Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	28June2016
From	Laurie Muldowney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208271
Supplement#	
Applicant	Salix Pharmaceuticals, Inc
Date of Submission	19Jun2015
PDUFA Goal Date	Original: 19Apr2016
	Extended: 19Jul2016
Proprietary Name / Established (USAN) names	Relistor®/methylnaltrexone bromide
Dosage forms / Strength	Oral tablet/150mg (dosing regimen: 3 tablets once daily)
Proposed Indication(s)	1. Opioid-induced constipation in adult patients with chronic non-cancer pain
Recommended:	<i>Approval</i>

1. Introduction

On June 19, 2015, Salix Pharmaceuticals Inc. (the Applicant) submitted a New Drug Application (NDA) to support marketing approval of Relistor (methylnaltrexone bromide) oral tablets for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain (CNCP). Relistor (methylnaltrexone bromide) subcutaneous injection is currently approved for the following indications under NDA 021964:

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

The review of this Application was conducted as a Standard review.

Efficacy from a single phase 3 trial was submitted to support the new dosage form. The Applicant provided data characterizing the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of subcutaneous (SC), intravenous and oral dosage forms; allowing extrapolation of efficacy results from studies for the approved Relistor® to support approval for the oral dosage form. Similarly, the Applicant did not provide long-term safety data for methylnaltrexone oral tablets; however, the long-term safety of the oral tablets is supported by the clinical studies for the approved Relistor® product which included exposures up to 48 weeks.

A major theme in the review of the efficacy for this application was whether the results of the phase 3 trial (MNTX3201) could support the approval of methylnaltrexone bromide oral tablets, given that the Agency disagreed with the prespecified primary endpoint. The current standard for clinical trials for drugs intended to be used chronically in the management of OIC

in CNCP includes an overall responder endpoint from a well-controlled clinical trial with a 12 week primary analysis period. The Applicant's phase 3 trial included only a 4 week primary analysis period, and the prespecified primary endpoint was the percentage of dosing days that resulted in rescue free bowel movements (RFBMs) within 4 hours of dosing during weeks 1 – 4, which was not felt to be clinically meaningful in this chronic condition. The Applicant included a key secondary endpoint, however, that assessed the proportion of subjects who responded to study drug during weeks 1-4. The approved Relistor® SC was approved on a similar 4-week responder endpoint, so while our current standards require a 12 week responder endpoint, the responder endpoint was ultimately determined to be acceptable. There were concerns raised by the statistical reviewers, as to whether the secondary endpoints could be reviewed based on the Applicant's selected multiplicity adjustment procedure which required the Applicant to win on the primary endpoint with all doses studied in order to consider the secondary endpoints (only the 2 higher doses won on the primary endpoint). Ultimately it was decided that the responder endpoint could be reviewed and would be considered as the relevant endpoint for determination of approvability.

All the review disciplines recommend in favor of approval, and I agree with their recommendations. A single post-marketing requirement (PMR) is needed to conduct a postmarketing observational study comparing methylnaltrexone bromide oral tablets to other non-PAMORA treatments of OIC, comparing the incidence of major adverse cardiovascular events. This PMR is to address cardiovascular safety concerns with this class of drugs, peripherally acting mu-opioid receptor antagonists (PAMORAs), and not related to a safety signal identified during the oral methylnaltrexone bromide clinical development program.

This memo summarizes the information contained in NDA 208271 and discusses the recommendations made by each review discipline.

2. Background

Clinical Background:

Opioid-induced constipation (OIC) is a frequent complication of chronic opioid use. Opioids exert their analgesic effects via opioid receptors (mu, delta, and kappa), with the majority of approved opioids exerting their primary activity at mu receptors. In the gastrointestinal system, mu-opioid receptors are localized to the mesenteric and submucosal plexus. Mu opioid agonists commonly inhibit gastric emptying, increase absorption and decrease secretion in both the large and small intestine, and delay small intestinal and colonic transit. As such, chronic opioid use may result in increased gastroesophageal reflux, hard dry stools, incomplete evacuation, straining, and abdominal distension.

Treatment of OIC includes non-pharmacologic therapies (e.g., dietary changes, manual evacuation), over the counter therapies (e.g., stool softeners, laxatives), and prescription therapies. There are currently 3 approved products on the market for the treatment of OIC in adult patients with chronic non-cancer pain. These approved therapies are:

- Amitiza® (lubiprostone) oral tablets, approved in 2013 for OIC (NDA 021908)
- Movantik® (naloxegol) oral tablets, approved in 2014 for OIC (NDA 204760)
- Relistor® (methylnaltrexone bromide) subcutaneous injection, approved in 2014 for OIC (NDA 021964)

Approval of methylnaltrexone bromide oral tablets would provide an alternative oral dosage form to the approved Relistor® SC. Availability of an oral tablet may provide additional convenience to patients currently receiving Relistor® SC and provide access to methylnaltrexone bromide to patients who are unwilling to use a subcutaneous formulation.

Regulatory Background:

Relistor® Subcutaneous Injection was first approved 24April 2008 under NDA 021964 for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Subsequently, a supplemental NDA was approved on 29September2014 for the indication of treatment of OIC in adults with CNCP. Prior to submission of this application, the Applicant had two preNDA meetings with the FDA which focused on the adequacy of study MNTX3201 to support approval of methylnaltrexone bromide oral tablets for OIC in CNCP.

A pre-NDA meeting was held on 07March2012. The Sponsor provided summary information on their single pivotal trial, MNTX3201. The Agency stated disagreement with the primary endpoint assessing RFBM within 4 hours of dosing, as this endpoint was not believed to be clinically meaningful. It was further noted that the lowest of 3 doses tested in study MNTX3201 (150 mg) failed to demonstrate a positive result on the primary endpoint. As such, and based on the sponsor's prespecified multiplicity adjustment, the Sponsor could not test secondary endpoints which may have more clinical meaningfulness.

A second preNDA meeting was held on 04November2015, in which the Sponsor proposed the same trial MNTX3201 to support approval of methylnaltrexone bromide oral tablets, and the same concerns were raised by the Agency. It was reiterated that the Agency did not agree that the prespecified primary endpoint of average percentage of dosing leading to RFBM within 4 hours dosing was appropriate for labeling, as it does not adequately define an overall responder. In order for the results of study MNTX3201 to support approval, the results of the prespecified analyses supporting the proposed dose would need to be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product.

The Application was received electronically on 19Jun2015. Submission of the NDA is based on the oral dosage form as an alternative to SC injection. The relevant data to support the NDA submission included oral clinical data from phase 3 Study MNTX3201, data characterizing the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of SC, intravenous, and oral dosage forms, and subcutaneous clinical data supporting the efficacy and long-term safety of methylnaltrexone bromide in OIC in CNCP.

Submission and Review:

The Application was received electronically on 19Jun2015, and the Application was granted a Standard Review status. The goal date was 19Apr2016.

All of the relevant review disciplines have written review documents. The primary review documents relied upon in my CDTL memo are listed below.

Table 1: Summary of Review Disciplines and Reviewers for NDA 208271

Review Discipline	Name(s) of Reviewers and Dates of Review(s)
Clinical (DGIEP)	D. Zand, MD, L. Muldowney, MD, dated 03June2016
Nonclinical (DGIEP)	S. Chakder, PhD, dated 23March2016
Clinical Pharmacology (OCP/DCP3) and Pharmacometrics	D. Jappar, PhD, J. Earp, PhD, N. Mehrotra, PhD, S.C. Lee, PhD, dated 08June2016
OPQ Review Drug Substance (OPQ/ONDP/DNDAP/ NDPBII)	S. Bain, PhD/D. Christner, PhD, dated 07March2016
OPQ Review Drug Product and Environmental Assessment (ONDP/DNDP II/ NDPB V)	S. Ibrahim, PhD/M. Rhee, PhD, dated 14March2016
OPQ Application Technical Lead (ONDP/DNDP II/ NDPBV)	D. Gromek-Woods, PhD, dated 14March2016
OPQ Microbiology and Process Review (OPF/Division of Process Assessment II/NDPBV)	B. Jiang, PhD/C.Cruz, PhD, dated 24February2016
OPQ Review Facility (OPF/DIA/GCB III)	M. Heayn, CSO/J. Williams PhD, dated 14March2016
Biopharmaceutics (ONDP/DB/BBII)	V. Kolhatkar, PhD/T.M. Chen, PhD, dated 09March2016
Statistics (DBIII)	S. Farr/A. Parfionovas/Y.F.Chen, dated 25June2016
Clinical Site Inspections (OC/DMPQ)	S. Leibenhaut, MD/S. Thompson, MD, dated 21Jan2016
Consultation review (DPMH)	E. Hausman, MD, H. Sachs, MD, dated 02February2016
Consultation review (DPMH)	M. Dinatale DO, T. Johnson, MD, dated 14March2016
Consultation review (DAAAP)	L. Kilgore, MD, J. Lloyd, MD, dated 21March2016
Labeling review (DMEPA)	S. Abraham RPh, L. Merchant, PharmD, dated 17February2016

DGIEP: Division of Gastroenterology and Inborn Errors Products, OPQ: Office of Pharmaceutical Quality, ONDP: Office of New Drug Products, DNDP: Division of New Drug Products, DNDAP: Division of New Drug Active Pharmaceutical Ingredient, OPF: Office of Process and Facilities, OCP: Office of Clinical Pharmacology, DCP3: Division of Clinical Pharmacology 3, DMEPA: Division of Medical Error Prevention and Analysis, DPMH: Division of Pediatric and Maternal Health

The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes selected information from the primary review documents.

3. CMC/Device

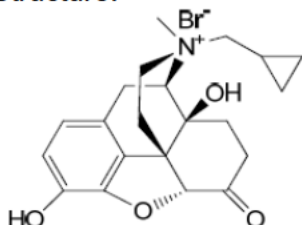
The quality reviewers have recommended approval of NDA 208271 with a drug product expiration dating period of 36 months, and I agree with their assessments. The quality reviewers concluded that there are sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance and drug product. The labeling and labels are deemed satisfactory from the CMC perspective. The Office of Facility and Process recommend approval for the facilities involved in the application, and the claim for a

Categorical Exclusion for the Environmental Assessment is granted. I have summarized the key review findings below. The reader is referred to the OPQ Integrated Quality Assessment review, dated 21March2016, for the complete information.

CMC/Drug Substance Quality Review

The active pharmaceutical ingredient (API) in the drug product is methylnaltrexone bromide.

Structure:



Molecular Formula: C₂₁H₂₆BrNO₄

Molecular Weight: 436.34

Chemical Names: 17-(Cyclopropylmethyl)-4,5a-epoxy-3,14- dihydroxy-17-methyl-6-oxomorphinan-17-ium Bromide (R)-N-(Cyclopropylmethyl)noroxymorphone Methobromide

The drug substance will be sourced from (b) (4), and Mallinckrodt, Inc. MO, USA. The detailed drug substance CMC information is provided in 3 DMFs:

- (b) (4)
- (b) (4) (Mallinckrodt)
- (b) (4) (Mallinckrodt)

These DMFs were reviewed by Dr. Sukhamaya Bain, Ph.D. and were found to be adequate to support approval. The quality reviewer commented that the application includes using drug substance manufactured (b) (4).

The Applicant provided X-ray Powder Diffraction (XRPD) data for all 3 sources which was reviewed and showed similar XRPD patterns. The drug substance quality reviewer concludes that methylnaltrexone bromide is controlled by adequate specifications that includes tests for appearance, identification, assay, impurities, (b) (4) water content, residue on ignition, loss on drying, residual solvents, specific optical rotation, (b) (4) content, particle size, (b) (4), pH (b) (4), and heavy metals.

CMC/Drug Product Quality Review

Methylnaltrexone bromide oral tablets, 150 mg, are white, round, biconvex, film coated tablets, debossed with "REL" on one side and plain on the other side. The drug product will be packaged in high-density polyethylene bottles (b) (4) and each bottle will include 2 silica gel desiccants. Inactive ingredients are silicified microcrystalline cellulose, microcrystalline

cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc. As described in the drug product quality review, the Applicant provides the description, components and composition of the drug product, including the function of each excipient in the proposed finished drug product. Concentrations of all excipients are below the IIG limits for oral administration with the exception of Silicified Microcrystalline Cellulose. The limits of Silicified Microcrystalline Cellulose were found to be

acceptable, (b) (4)

The finished product is manufactured by (b) (4) The drug product quality reviewer concluded that the Applicant has provided sufficient support of the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product. The proposed specifications for methylnaltrexone bromide tablets, 150 mg, are considered acceptable for assuring the identity, strength, purity, and quality of the drug product and for its intended use over the proposed shelf life. The Applicant provided a total of 24 months long-term and 6 months accelerated stability data which were determined to be sufficient to justify the proposed expiration dating of 36 months.

Facilities review/inspection

The Office of Process and Facility has issued an "approval" recommendation for all facilities involved in this NDA. Based on the initial risk assessment and further review of the firm's inspectional history and experience, a pre-approval inspection was not requested for any of the API facilities. Similarly, pre-approval inspections were not requested for the drug product facility or packaging and labeling facility due to recent applicable inspectional history and the results of the risk assessment. The reviews by Drs. J. Williams and M. Heayn concluded that there appear to be no risks to the manufacturing process or final product based on the results of recent facilities inspections and the inspectional history.

CMC/Manufacturing Process Review

The quality reviewers concluded that the Applicant has provided sufficient information to adequately define and justify the manufacturing process, with sufficient in process controls to ensure drug product quality. Therefore, from the manufacturing process perspective, the reviewers have recommended approval.

CMC/Biopharmaceutics Review

The biopharmaceutics reviewers recommend approval of this Application and found the proposed dissolution method, acceptance criteria and method validation to be acceptable. A BE study and dissolution testing in four media were conducted to provide bridging between the tablets manufactured by (b) (4) for the phase 3 study and (b) (4) for marketing. Methylnaltrexone bromide tablets manufactured by either process demonstrated rapid in vitro dissolution in all tested dissolution media.

CMC/Microbiology Review

According to the microbiology reviewer, Dr. Bo Jiang, Ph.D., Microbial limits test is included in the drug product specification, the test methods are in accordance with current USP <61> and USP <62>, and the acceptance criteria comply with USP <1111>, and are appropriate for a solid oral dosage form. The microbiology assessment overall recommendation is "Acceptable".

CMC/Environmental Assessment

The quality reviewers granted the Applicant's request for the categorical exclusion from the Environmental Assessment.

The CMC/quality reviewers have not recommended PMCs or PMRs.

4. Nonclinical Pharmacology/Toxicology

The nonclinical team has recommended approval, and I agree with the recommendation. For complete information, the reader is referred to the Pharmacology/Toxicology review by Dr. S. Chakder (primary/secondary review), dated 23March2016. I have summarized the key review findings below.

Nonclinical studies of methylnaltrexone bromide, including pharmacology, safety pharmacology, pharmacokinetics, metabolism and toxicology (general toxicology, genetic toxicology, carcinogenicity and reproductive toxicity) studies were submitted and reviewed under NDA 21964 for the approval of subcutaneous Relistor®. No new toxicology studies of methylnaltrexone were submitted under NDA 208271. The results of the toxicology studies from NDA 21964 were reviewed previously by Dr. Tamal Chakroborti and were found to be acceptable. In brief,

- The NOAEL from the 6-month repeat dose oral toxicity study in rats was 100 mg/kg/day which is approximately 13 times the clinical dose of 450 mg/day. The NOAEL from the 9-month repeat dose oral toxicity study in dogs was 60 mg/kg/day which is approximately 8 times the proposed clinical dose of 450 mg/day. These results indicate the proposed dose provides adequate safety margins.
- Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the in vivo mouse micronucleus test.
- Methylnaltrexone bromide did not produce any neoplasm in mice and rats in previously conducted 2-year carcinogenicity studies.
- Methylnaltrexone bromide had no adverse effect on fertility, reproductive performance, or embryofetal development in reproductive toxicology studies.

Since the approval of subcutaneous Relistor®, several nonclinical pharmacology studies were conducted, the results were submitted under NDA 208271. These were reviewed by Dr. S Chakder and were found to be acceptable. In brief,

- Methylnaltrexone and its metabolites were found to bind with μ - opioid receptors with high affinities (IC₅₀ values, 34 nM to 10.7 μ M).
- Methylnaltrexone and its metabolites had no significant effect on hERG currents at concentrations up to 100 μ M in an in vitro hERG assay in human embryonic kidney cells.

No novel excipients are used in the formulation. The nonclinical review states that the specifications for the drug-related impurities for the drug substance are consistent with the ICH Guidance Q3A (R2) specification limits and are acceptable. Similarly, the specifications for the two residual solvents, (b) (4) are in compliance with the ICH Q3C (R5) acceptance levels and are acceptable. Long-term stability studies were conducted with the original formulation of 150 mg methylnaltrexone bromide tablets. An unknown impurity was identified as (b) (4), which is similar to the known drug substance process impurity and degradant reported in NDA 21964 for SC Relistor. This impurity is controlled at levels of not more than (NMT) (b) (4) %, which the nonclinical review reports is acceptable as it is consistent with ICHQ3B(R2) qualification threshold for impurities.

In summary, the nonclinical review concluded that the nonclinical safety of oral methylnaltrexone has been adequately addressed. No nonclinical approval issues were identified. Recommendations for the labeling, to include updating to PLLR format, were provided to the Applicant.

5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review by Dr. D. Jappar, dated 08June2016, for complete information. The Office of Clinical Pharmacology considers the submission acceptable from a clinical pharmacology standpoint to support this NDA, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the labeling. At the time of this review, the Applicant has accepted the review team's recommended changes to the Clinical Pharmacology section of the labeling, however, a finalized label has not yet been agreed upon.

Approvability of NDA 208271 is based on the development program of an oral methylnaltrexone bromide tablet as an alternative to the approved subcutaneous formulation. As such, the Applicant conducted only a single adequate and well controlled phase 3 study of oral methylnaltrexone bromide, MNTX3201. In addition to the phase 3 study, in support of this NDA the Applicant submitted multiple clinical pharmacology studies, specifically: Eight (8) in-vitro studies (Table 2 below), 7 in-vivo clinical pharmacology studies (Table 3 below), and PK/PD modeling to evaluate the exposure-response relationship. The Applicant provided data characterizing the pharmacokinetic (PK) relationship of subcutaneous (SC), intravenous and oral dosage forms. Results of PK/PD modeling were also provided, in attempt to demonstrate systemic exposure-response relationships for methylnaltrexone, however there was limited exposure data provided making definitive conclusions on exposure response challenging; however, the Office of Clinical Pharmacology agrees with the proposed dose for marketing based on the information provided. I summarized key findings from Dr. Jappar's review below.

Table 2: Summary of In-Vitro Studies in Support of NDA 208271

Study Identifier	Type of Study	Title/Objective(s) of the Study
XS-0641	Protein Binding	Assessment of methylnaltrexone sulfate, methyl-6 α -naltrexol, and methyl-6 β -naltrexol protein binding in human plasma
XT128007	Transporter	Evaluation of Methylnaltrexone as an Inhibitor of Human P-gp, BCRP, OCT2 and MRP2 and Substrate of Human BCRP, MRP2, OATP1B1, OATP1B3, OAT1 and OAT3 Transporters
XS-0621	Transporter	Evaluation of Methylnaltrexone as an Inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K and Substrate of MATE1 and MATE2-K; Evaluation of Methylnaltrexone Sulfate, Methyl-6 α -Naltrexol and Methyl-6 β -Naltrexol as Inhibitors and Substrates of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K
XT123038	CYP induction by metabolites	Evaluation of Methylnaltrexone Sulfate, Methyl-6 α -Naltrexol and Methyl-6 β -Naltrexol as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
XT125033	CYP inhibition by metabolites	In Vitro Evaluation of Methylnaltrexone Sulfate, Methyl-6 α -naltrexol and Methyl-6 β -naltrexol as Inhibitors of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
RPT-63601	Direct Glucuronidation	Evaluation of the Potential For Direct Glucuronidation of N-Methylnaltrexone (MNTX) In Human, Sprague-Dawley Rat, And Beagle Dog Microsomes
RPT-63643	Metabolism by CYP450	Identification of Cytochrome P450 Drug-Metabolizing Enzymes Involved in the Metabolism of N-Methylnaltrexone Utilizing CDNA-Expressed Human Enzymes
RPT-63756	Metabolic Stability	Metabolic Stability Study of Methylnaltrexone in Rat, Dog, And Human Hepatic Microsomes

Source: Clinical Pharmacology Review by D. Jappar, PhD; Table 2

Table 3: Summary of In-Vivo Clinical Pharmacology Studies in Support of NDA 208271

Study #	Objective(s)	Study Design	Test product; Dosage Regimen; Route of administration	Subjects
MNPK1001	Formulation Exploration BE study (includes pivotal BE study)	Open-label, multiple-cohort, single-dose, two-way crossover	Single doses of 450 mg (3 x 150 mg) MNTX oral tablets from 6 test formulations. The reference tablet was the (b) (4) formulation used in Study MNTX 3201	180 healthy subject
MNFE1001	Food effect	Open label, single dose, crossover	Single dose of oral 450 mg (3x150 mg) MNTX (b) (4) tablets (TBM)	32 Healthy subjects
MNPK1114	Food effect	Open label, single dose, crossover	Single dose of 450 mg (3 x 150 mg) MNTX oral tablets (b) (4) formulation)	32 Healthy subjects
MNPK1004	Hepatic impairment	Open label, single dose, parallel group	Single dose of 450 mg (3 x 150 mg) MNTX oral (b) (4) tablets (TBM)	24 Hepatic impaired subjects (mild, moderate, and severe) and matched healthy subjects
MNOC1111	PK, efficacy and Safety in Patient population, Phase 1b.	Open Label Phase: Open-label, single SC dose, to assess for clinical response Double Blind Phase (OL responders only): Randomized, placebo-controlled, single-dose	Open Label Phase: • Single-dose of 12 mg SC MNTX Double Blinded Phase: • 450 mg (3 x 150 mg) MNTX (b) (4) tablets (TBM) • 450 mg (3 x 150 mg) MNTX (b) (4) tablets (phase 3 formulation) • matching placebo tablets	138 Patients with chronic non-cancer pain who have OIC
MNPK1117	Relative BA to SC formulation	Open label, cross-over	Single doses of oral MNTX tablets • 150 mg (1 x 150 mg tablet) • 300 mg (2x 150 mg tablets) • 450 mg (3 x 150 mg tablets) Single doses of MNTX SC 12 mg	48 Healthy subjects
MNPK1118	Multiple dose PK study (stage 1) Relative BA study (stage 2)	Open-label, 2-stage, single and multiple-dose	Stage 1: Once daily doses of 450 mg (3 x 150 mg) MNTX oral film-coated tablets for 7 days; Stage 2: Single dose of 450 mg (3 x 150 mg) MNTX oral film-coated tablets (test formulation) single dose of 450 mg (3 x 150 mg) MNTX uncoated oral tablets with (b) (4) (phase 3 formulation)	16 healthy subjects in Stage 1 16 healthy subjects in Stage 2
MNTX 3201	Efficacy, safety & tolerability	Randomized, double-blind, parallel-group, placebo-controlled	Oral MNTX 150 mg tablets (b) (4) formulation) or placebo; Randomized 1:1:1:1 to 150 mg, 300 mg, 450 mg, or placebo; Dosing QD during the first 4 weeks and PRN for the remaining 8 weeks	804 Patients with chronic non- cancer pain who have OIC

Source: Clinical Pharmacology Review by D. Jappar, PhD; Table 1.

Pharmacokinetics:

Between oral doses of 150 mg and 450 mg, methylnaltrexone has an approximately dose proportional increase in C_{max} and AUC with no significant accumulation following once daily dosing of 450 mg methylnaltrexone bromide tablet. Steady state PK is reached within approximately 7 days.

Absolute bioavailability of oral methylnaltrexone bromide was not evaluated. The relative bioavailability of the proposed oral formulation was compared to the currently approved subcutaneous formulation in study MNPK1117, a randomized, open-label, single-dose, crossover study in 48 healthy subjects. The C_{max} after oral route of administration at all dose levels were lower than SC administration. The AUC_{0-∞} after oral methylnaltrexone bromide of 150 mg and 300 mg was less than the AUC_{0-∞} after methylnaltrexone bromide SC 12 mg, while that of 450 mg oral methylnaltrexone bromide was 1.2-fold greater than that of SC methylnaltrexone bromide 12 mg. Compared to SC route of administration, the dose corrected bioavailability of oral methylnaltrexone bromide was 3-4%. Summary PK results from this study are shown in Table 4 below.

Table 4: Single-Dose Pharmacokinetic Parameters for Oral and Subcutaneous MNTX: Study MNPK1117

	MNTX 150 mg Tablet (N = 16)	MNTX 300 mg Tablet (N = 16)	MNTX 450 mg Tablet (N = 16)	MNTX 12 mg SC Injection (N = 48)
C _{max} (ng/mL) ^a				
Mean (SD)	13.22 (15.17)	26.22 (18.40)	39.89 (32.11)	174.01 (61.42)
Dose proportionality ratio (90% CI) ^b	--	1.13 (0.76, 1.68)	1.11 (0.75, 1.65)	--
AUC _{0-∞} (ng.h/mL) ^a				
Mean (SD)	106.87 (64.77)	231.24 (115.98)	373.32 (207.36)	269.09 (45.14)
Dose proportionality ratio (90% CI) ^b	--	1.10 (0.82, 1.49)	1.13 (0.83, 1.52)	--
AUC ₀₋₄ (ng.h/mL) ^a				
Mean (SD)	104.65 (64.66)	229.37 (116.27)	366.67 (205.71)	267.87 (44.94)
Dose proportionality ratio (90% CI) ^b	--	1.12 (0.83, 1.52)	1.13 (0.84, 1.54)	--

^a Mean values are arithmetic means unless otherwise specified

^b ratios of dose-normalized geometric means for parameters from 300 mg and 450 mg doses relative to the 150 mg dose

Source: Clinical Pharmacology Review by D Jappara, PhD; Table 11

No mass balance study was conducted with methylnaltrexone bromide oral tablets. A mass balance study was previously conducted with an IV formulation which demonstrated that 53.6% of the dose was excreted in the urine and 17.3% was excreted in the feces up to 168 hours post-dose. The relative bioavailability of oral tablets compared to IV formulation was not evaluated; however, thus the contribution of renal vs. hepatobiliary clearance cannot be determined.

Administration of oral methylnaltrexone bromide with a high-fat breakfast reduced the AUC and C_{max} by 45% and 60%, respectively and delayed the T_{max}, compared to administration in the fasted state. As such, the Applicant proposes taking the tablet on an empty stomach in the label, and the clinical pharmacology reviewer agrees with this recommendation. Methylnaltrexone bromide is mainly metabolized by sulfotransferase and aldo-keto reductase 1C enzymes, and is not substantially metabolized by CYP enzymes.

The concentrations of methylnaltrexone and its 3 metabolites (methylnaltrexone-sulfate (M2), methyl-6α naltrexol (M4), and methyl-6β naltrexol (M5)) in plasma and urine were

measured. The AUC ratio of metabolites to the parent drug at steady-state is higher after oral administration than SC administration based on cross study comparisons. This is not unexpected given the anticipated hepatic first pass effect with oral administration.

Dose-Exposure-Response Relationship

The Clinical Pharmacology reviewer agrees with the proposed dose of 450 mg, based on the safety and efficacy results from three dose levels of methylnaltrexone bromide (150 mg, 300 mg, and 450 mg) studied in study MNTX3201. Specifically, a dose proportional increase in the proportion of subjects responding to study drug was observed over 150 mg to 450 mg. While direct cross study comparisons for efficacy cannot be made, the efficacy of the 450 mg dose appears less than that of the approved 12 mg subcutaneous dose based on similar responder analyses assessed during their respective pivotal trials.

As stated above, PK exposures had approximately linear increases from 150 mg to 450 mg. However, as shown in Table 5 below, above 450 mg there was a less than proportional increase, suggesting that increasing doses above 450 mg (the proposed dose for marketing) may not yield higher exposures. The AUC is similar between the proposed oral dose of 450 mg compared to the approved 12 mg subcutaneous dose, but the C_{max} is approximately 4-fold higher with the subcutaneous dose. PK data was not collected in the phase 3 trial for exposure response analyses, however, early phase 1 and phase 2 studies suggest higher efficacy with increased exposures. These results are limited, however, as the sponsor did not include responder analyses in these studies, and patient populations outside the population of interest were included (e.g., methadone maintenance population). The limited exposure data provided by the Applicant makes drawing definitive conclusions on exposure response challenging.

Table 5: Pharmacokinetic Exposures of Methylnaltrexone Across the Range of Studied Oral Doses and 12 mg Subcutaneous Dose

	150 mg PO	300 mg PO	450 mg PO DC	600 mg PO	12 mg SC
AUC (ng·hr/mL)	107	231	105 ¹ - 373 ²	105 ³	186 - 269
C _{max} (ng/mL)	13.2	26.2	35 ¹ - 48 ³	44 ³	133 - 174

(Source: Applicant's Summary of Clinical Pharmacology, Studies ¹MNOC1111, ²MNPK1117, ³MNTX-2201)

Source: Clinical Pharmacology Review by D. Jappar, PhD; Table 5.

The majority of adverse events do not appear to have a dose-response; however, abdominal pain and diarrhea occurred more frequently at higher doses. The rate of these GI related AEs appears less with the proposed 450 mg oral dose than was observed in the pivotal trials with subcutaneous Relistor® 12mg. This is not unexpected, given the higher exposures shown with the subcutaneous formulation.

In total, the Applicant's exposure-response data was limited; however, the dose response data support the 450 mg dose based on higher efficacy compared to lower doses and an acceptable safety profile. It appears that the 450 mg oral dose may have slightly lower

efficacy but improved tolerability compared to Relistor® SC and is an acceptable dose for marketing.

Relative BA/BE:

The phase 3 study MNTX3201, used a 150-mg tablet formulation manufactured by (b) (4). The sponsor later developed a film-coated, (b) (4) tablet formulation (b) (4). The Clinical Pharmacology reviewer states that the to-be-marketed formulation is bioequivalent to the phase 3 formulation. This was demonstrated in study MNPK1001 and was supported by results from study MNOC1111.

Specific Populations:

The exposure of methylnaltrexone in subjects with hepatic impairment is significantly higher than the exposure in subjects with normal hepatic function. The mean C_{max} was 1.7-, 4.8- and 3.7- fold higher in subjects with Child-Pugh A, B and C hepatic impairment compared to subjects with normal hepatic function following single oral dose administration of 450 mg. The AUC was similar in subjects with Child-Pugh A and healthy subjects, but the AUC in subjects with Child-Pugh B and C hepatic impairment were approximately 2.5- and 2.2- fold higher than the healthy subjects, respectively.

The Applicant is proposing no dose adjustment in patients with Child-Pugh Class A and proposing reduction to 150 mg daily in patients with Child-Pugh Class B and C. The Clinical Pharmacology reviewer finds the proposal to not dose adjust for Child-Pugh Class A acceptable, as the 1.7-fold higher C_{max} is still less than the C_{max} of the currently marketed subcutaneous formulation, thus the safety profile with the higher exposure is acceptable. The dose adjustment for Child-Pugh Class B and C is appropriate, as the expected exposures would be significantly greater than that of the currently marketed SC formulation.

The Applicant did not complete a dedicated PK study to evaluate the impact of renal impairment on PK, however, a renal impairment study was completed previously with subcutaneous methylnaltrexone bromide. In this study, AUC increased by 30%, 75% and 90% in patients with mild, moderate and severe renal impairment compared to subjects with normal renal function. The Applicant proposes (b) (4).

However, in order to ensure the exposure does not greatly exceed those with a known safety profile, the Clinical Pharmacology reviewer recommends dose reduction to 150 mg daily in patients with moderate or severe renal impairment.

QT Studies:

No QT studies were conducted with oral methylnaltrexone bromide. The Clinical Pharmacology reviewer concluded that the potential of oral Relistor to prolong the QT is minimal, based on the information from the previous submission for Relistor SC and the PK exposures of oral methylnaltrexone bromide. Specifically, the C_{max} of the 450 mg oral tablet is about 22 fold lower than the C_{max} of 0.64 mg/kg IV infusion that did not prolong QT in previous studies.

Drug-Drug Interactions:

No in-vivo drug-drug interaction studies were conducted for this submission. The results of in-vitro studies in this submission did not suggest need for any in-vivo drug-drug interaction study.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application, because methylnaltrexone bromide is not intended as an antimicrobial product.

7. Clinical/Statistical- Efficacy

The clinical reviewer and statistical team have recommended approval, and I agree with the recommendation. For complete information, the reader is referred to the Clinical review by Dr. D. Zand, dated 03June2016 and the Statistical review by Drs. S. Farr, A. Parfionovas, and Y.F.Chen, dated 25June2016 for complete information. I have summarized the key review findings below

The Applicant's submission is based on the development of methylnaltrexone bromide oral tablets as an alternative to the approved Relistor® subcutaneous formulation (NDA 21964) in the treatment of OIC in patients with CNCP. As such, the Applicant completed only a single phase 3 study, MNTX3201, to demonstrate the efficacy of methylnaltrexone bromide tablets. In addition to Study MNTX3201, the Applicant completed multiple PK/PD studies to evaluate the relative bioavailability between different dosage forms and formulations as well as PK/PD modeling allowing extrapolation of data from the SQ program to support approval of methylnaltrexone bromide oral tablets. Only Study MNTX3201, "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" is discussed in this section.

The Food Drug and Cosmetics Act requires that to obtain marketing approval, manufacturers must demonstrate the effectiveness of their product through adequate and well-controlled studies, which has generally been interpreted to mean 2. FDA has been flexible within the limits imposed, however, and in some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses or dosage forms. The Applicant completed numerous PK/PD studies, and it is appropriate to consider the phase 3 studies for Relistor® as supportive evidence of the efficacy of methylnaltrexone bromide oral tablets in OIC in patients with CNCP. Thus a single adequate and well-controlled study is acceptable.

Regulatory Background:

Study MNTX3201 is a double-blind, randomized, placebo-controlled trial which randomized 803 adult patients with OIC to one of 3 doses of methylnaltrexone bromide (150 mg, 300 mg, or 450 mg) or placebo. The primary endpoint of this study was the average percentage of dosing days that resulted in a RFBM within 4 hours of dosing during the study length of 28 days, comparing methylnaltrexone bromide tablets and placebo. The current standard for the design of an adequate and well-controlled study for drugs intended to be used chronically in the management of OIC in adults with chronic, non-cancer pain is a 12-week randomized, controlled trial in order to evaluate the durability of efficacy. The recommended primary endpoint for such studies is the proportion of subjects who are weekly responders for at least

9 of the 12 weeks, including 3 of the last 4 weeks of the 12-week study period, where a weekly responder is defined as ≥ 3 RFBMs/week for each week of the study, with an increase of ≥ 1 RFBM/week over baseline

The design and endpoints of this study have been discussed with the Applicant in 2 previous pre-NDA meetings on 07March2012 and 04November2014, which are summarized below.

- 07March2012: multiple concerns were conveyed to the Applicant regarding study MNTX3201. Specifically, a clinically relevant endpoint was not evaluated over an adequate treatment duration (i.e. 12 weeks) and the primary endpoint assessing RFBM within 4 hours of dosing is not acceptable. In addition, it was noted that the 150 mg dose regimen failed to demonstrate a positive result assessed by the primary endpoint based upon the proposed Hochberg multiplicity adjustment procedure, and since not all three doses showed significant results and Hochberg procedure is not a separable procedure, no alpha level was left to test secondary endpoints. The Division recommended the sponsor conduct 2 independent phase 3 trials to demonstrate the efficacy and safety of the proposed product in OIC.
- 04November2014: the Applicant again proposed that study MNTX3201 established sufficient basis for submission of an NDA for oral methylnaltrexone bromide as an alternative to the approved SQ injection, with reliance on PK/PD data and data from the SQ program. The Agency reiterated that the current standards for the design of trials for new drugs to treat OIC in NCP include a 12-week primary analysis period, but acknowledged that these standards have changed since the completion of study MNTX3201 and approval of Relistor® SQ. Relistor® was approved based on a primary endpoint of the proportion of patients with ≥ 3 spontaneous bowel movements (SBMs) per week during the 4-week double-blind period.

The Agency reiterated disagreement with the prespecified primary endpoint (average percentage of dosing days that resulted in a RFBM within 4 hours of dosing over 28 days) as it does not adequately define an overall responder and stated that, *"in order for Study MNTX3201 to support approval, the results of the prespecified analyses supporting the proposed dose would need to be statistically valid, allowing for evaluation of key secondary analyses of interest for purposes of ultimately approving and labeling the product."*

Study MNTX3201 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of oral MNTX 150 mg, 300 mg, and 450 mg versus placebo in the treatment of 804 adult patients with chronic nonmalignant pain who have OIC. The primary efficacy endpoint was the average percentage of dosing days resulted in RFBMs within 4 hours of dosing during Weeks 1-4. The mean percentages of dosing days that resulted in RFBMs within 4 hours of dosing during Weeks 1 through 4 were 18.2% in the placebo arm compared to 27.4% in the 450 mg/day group (9.1% difference from placebo, $p < 0.0001$). As previously stated, the prespecified primary endpoint is not clinically meaningful, as it does not adequately define an overall responder. As such, it will not be considered for labeling.

As seen in Table 6 below, the results did not reach statistical significance for the 150 mg dose (2.8% difference from placebo, $p = 0.3076$). There were concerns raised by the statistical reviewers, as to whether the secondary endpoints could be reviewed based on the Applicant's

selected multiplicity adjustment procedure (Hochberg) which requires all three doses to show significant results in order to test secondary endpoints. Ultimately it was decided that the responder secondary endpoint could be reviewed and would be considered as the relevant endpoint for determination of approvability.

Table 6: Percentage of Dosing Days that Resulted in RFBMs within 4 Hours of Dosing During Weeks 1 - 4

Percentage of Dosing Days that Resulted in RFBMs within 4 hours of Dosing During Weeks 1-4	Dose MNTX			
	150 mg	300 mg	450 mg	Placebo
Intention-to-Treat Population (ITT)				
n	201	201	200	201
Mean percentage(SD)	21.05 (20.1116)	24.64 (21.311)	27.40 (23.453)	18.18 (16.995)
Median percentage (min, max)	14.81 (0.0,96.4)	21.43 (0.0,92.9)	23.54 (0.0,100)	14.29 (0.0,92.9)
LS mean	21.06	24.75	27.37	18.23
LS mean difference (vs. placebo) ^a	2.83	6.51	9.13	--
95% CI for difference (vs placebo) ^a	-1.21,6.86	2.47,10.55	5.09,13.18	--
Raw p-value (vs. placebo)	0.3076	0.0339	0.0043	--

Source: Clinical Review, Dr. D. Zand, Table 22. (Taken from Table 13, MNTX3201 Clinical Study Report)

^a From ANCOVA model with treatment as effect and analysis region covariate

The first key secondary endpoint was the proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as ≥ 3 RFBMs/week, with an increase of ≥ 1 RFBM/week over baseline, for ≥ 3 out of the first 4 weeks of the treatment period. A RFBM was defined as a bowel movement without laxative use within 24 hours prior to bowel movement. The proportion of responders during Weeks 1 through 4 were significantly greater in the methylnaltrexone bromide 450 mg/day group compared with the placebo group ($p = 0.0052$, as shown in Table 6 below.

Table 7: Responder Endpoint: Proportion (%) of Subjects Responding to Study Drug during Weeks 1–4 (ITT Population) Using Worst Case Approach^a

Proportion of Subjects Responding to Study Weeks 1-4	Dose MNTX			
	150 mg	300 mg	450 mg	Placebo
n	201	201	200	201
Yes-n (%)	86 (42.8%)	99 (49.3%)	103 (51.5%)	77 (38.3%)
Percentage Difference (vs Placebo)	4.5%	10.9%	13.2%	
95% CI for Odds Ratio	0.82, 1.84	1.04, 2.32	1.19, 2.65	
Raw p-value (vs. Placebo)	0.3185	0.0321	0.0052	

Source: Adapted from Table 14 MNTX3201 CSR

^a Worst case approach: missing weeks were classified as nonresponse for that week.

The statistical reviewer performed independent analyses of the responder endpoint using the Applicant's data and the preferred statistical test for analyzing binary data with stratification (Cochran-Mantel-Haenszel (CMH)) instead of logistic regression analysis, as performed by the Applicant. Dr. Farr's results were similar to the Applicant's reported results and showed a

statistically significant higher proportion of responders with methylnaltrexone bromide 450 mg compared to placebo (difference from placebo 13.2%, $p = 0.008$).

The Applicant's worst case approach classified missing weeks as nonresponse for that week; however, it was not clear whether this approach still included adjustment for missing diary data during a week in which there was 4 or more days of non-missing data in a week. The following information request was sent to the Applicant on 10June2016:

Perform a re-analysis of the proportion of subjects who responded to study drug during Weeks 1 to 4, where a responder is defined as having $\geq$ RFMB/week, with ≥ 1 RFMB/ week increase over baseline, for ≥ 3 out of the first 4 weeks. Treat patients who had 4 or more days of missing data in a week as non-responders for that week (i.e., worst case approach). For those patients who had more than 3 days of non-missing data in a week, do not input data for the missing days, rather present the data based on the actual number of bowel movements in a week to define a weekly responder. In other words, do not apply the following formula: $7 \times \text{total \# of RFMBs in a week} / \text{all non-missing assessment days in the given week}$.

In response, the Applicant performed the requested analysis and provided it in a response to information request dated 14June2014. The results showed the proportion of responders during Weeks 1 through 4 remained significantly greater in the methylnaltrexone bromide 450 mg/day group compared with the placebo group, as shown in Table 8 below ($p = 0.0050$).

Table 8: Proportion (%) of Subjects Responding to study drug during Weeks 1 to 4 (ITT)

Responders [1]	Placebo (N = 201)	MCA-728 150 mg (N = 201)	MCA-728 300 mg (N = 201)	MCA-728 450 mg (N = 200)
No Adjustment for Missing Diary Data Approach [2]				
Yes - n (%)	76/201 (37.8%)	84/201 (41.8%)	99/201 (49.3%)	102/200 (51.0%)
% Difference (vs Placebo)		4.0%	11.4%	13.2%
95% CI for % Diff. (vs Placebo)		(-5.6%, 13.5%)	(1.0%, 21.1%)	(3.5%, 22.8%)
Odds Ratio (OR/Placebo) [2]		1.20	1.59	1.78
95% CI for Odds Ratio [2]		(0.80, 1.80)	(1.06, 2.38)	(1.19, 2.66)
P-value (vs Placebo) [2]		0.3740	0.0245	0.0050

[1] Responder was defined as having ≥ 3 RFMBs/week and ≥ 1 RFMB/week increase from baseline, for at least 3 weeks of Weeks 1 - 4. The counts of RFMBs were not adjusted for missing diary days and for any week where a subject completed less than 4 diary days, that week was set to non-response. A RFMB was a bowel movement without laxative use within 24 hrs prior to the bowel movement.

[2] Based on logistic regression model with treatment as effect and analysis region as a covariate.

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The statistical reviewer also performed an independent analysis using the above described re-calculation for the responder's endpoint. According to the reviewer, the status of five patients was affected by the modified definition compared to the original dataset. The proportion of the patients and the p-values using the new method of calculation were consistent with the sponsor's findings. Ultimately the statistical review team concluded that "After thorough review by mainly considering the efficacy of the Relistor, the 450 mg was determined to be statistically significant compared to Placebo ($p=0.005$ and $p=0.008$, Sponsor's and reviewer's assessments, respectively)."

The Applicant's secondary responder endpoint is considered clinically meaningful, as it defines an overall responder for the study duration, however, it is not identical to the responder endpoint used for Relistor® SC approval. The responder endpoint for Relistor® SC was defined as the proportion of subjects with ≥ 3 RFMBs/week with study drug over Week 1 to 4, not 3 out of 4 weeks. In response to an information request (IR) dated 11 March 2016, the sponsor performed an additional statistical analysis for the overall proportion responders using the endpoint used as the basis of approval for Relistor® SC). The results are summarized in Table 7 below.

Table 9: Overall Proportion of Patients with ≥ 3 RFBM during the 4-week double blind study

Subjects Achieving ≥ 3 RFBMs/Week	MNTX 150 mg N=201	MNTX 300 mg N=201	MNTX 450 mg N=200	Placebo N=201
Double-Blind Treatment Period				
Yes – n/N (%)	114/196 (58.2%)	120/194 (61.9%)	120/193 (62.2%)	107/200 (53.5%)
% Difference (vs. Placebo)	4.7%	8.4%	8.7%	
95% CI for % Diff (vs. Placebo)	(-5.1%, 14.4%)	(-1.4%, 18.1%)	(-1.0%, 18.4%)	
Odds Ratio (OM/Placebo) [1]	1.23	1.40	1.49	
95% CI for Odds Ratio [1]	(0.82, 1.83)	(0.94, 2.10)	(0.99, 2.24)	
P-value (vs. Placebo) [1]	0.3116	0.1016	0.0541	

Source: Efficacy Information Amendment 1.11.3, dated 11Mar2016

As shown above, in the 450 mg treatment arm, 62.2% of patients had ≥ 3 SBMs/week compared to 53.5% in the placebo arm (difference from placebo 8.7%, $p = 0.0541$). By contrast, in the Relistor® SC pivotal trial, 59% of patients receiving Relistor 12 mg had ≥ 3 SBMs/week compared to 38% in the placebo group (difference from placebo 20%, $p < 0.001$). Cross-study comparisons should be interpreted with caution, but these data suggest that the efficacy with 450mg may not be quite as effective as with Relistor® SC.

The Applicant's trial included a 4-week primary analysis period, however, patients continued with double-blind treatment through week 12, and the sponsor assessed the proportion of responders over the 12-week period, and there was a greater proportion of overall responders in patients receiving methylnaltrexone bromide 450mg compared to placebo (42.0% compared to 29.4%) as is shown in Table 8 below. Dosing was PRN during weeks 5 – 12, which may confound the interpretation of these results, however, these results are consistent with the 4-week responder endpoint and suggest a durability of response over 12-weeks.

Table 10: Overall Responders – Proportion (%) of Subjects Responding to Study Drug for ≥ 9 of 12 Weeks

Responders ^a	Placebo	MNTX 150 mg	MNTX 300 mg	MNTX 450 mg
N	201	201	201	200
LOCF Approach^b				
Yes, n (%)	72 (35.8)	85 (42.3)	85 (42.3)	102 (51.0)
Percentage Difference (vs Placebo)	—	6.5	6.5	15.2
P-value (vs Placebo) ^c	—	0.1545	0.2166	0.0016
Worst Case Approach^d				
Yes, n (%)	60 (29.9)	69 (34.3)	67 (33.3)	81(40.5)
Percentage Difference (vs Placebo)	—	4.5	3.5	10.6
P-value (vs Placebo) ^c	—	0.2907	0.5478	0.0211

Source: Applicant MNTX3201 CSR, Table 14.2.5.5

^a Response was defined as ≥ 3 RFBMs per week, with an increase of ≥ 1 RFBM over baseline for the specific week, for ≥ 9 of 12 Weeks.

^b LOCF approach: for Weeks 1 – 2, the last nonmissing 4 days with diary data was imputed for the week with < 4 diary days. For Weeks 5 – 12, the last nonmissing weekly number of RFBMs was applied to any missing weeks.

^c based on logistic regression model with treatment as effect and analysis region as a covariate.

^d Worst case approach: missing weeks were classified as nonresponse for that week.

In summary, while we do not agree with the prespecified primary endpoint, the Applicant's results were highly statistically significant for the 450mg dose with their prespecified primary endpoint. The key secondary responder endpoint is the most clinically relevant for this indication, and while current standards are for a minimum primary efficacy analysis period of 12 weeks, as the SQ formulation was approved previously based on a 4-week endpoint and the Applicant is relying in part on this data, a 4-week primary analysis period is acceptable. While there was concern regarding the multiplicity procedures and whether the secondary endpoints could be assessed, it was ultimately decided that because the secondary responder endpoint was most clinically meaningful to the review team, it should be the endpoint considered when assessing the efficacy of the product. Oral methylnaltrexone bromide 450mg was statistically significantly better than placebo with their key secondary responder endpoint. Posthoc cross study comparison with Relistor® SC (using the same endpoint definition from the pivotal SC studies) suggested the oral formulation to be slightly less effective than the SQ formulation, however, cross study comparisons should be considered with caution. When looking at secondary endpoints over 12 weeks, the 450 mg dose was nominally statistically significantly more effective than placebo, which provided reassurance that the oral formulation is effective beyond the first few weeks. In total, the data supported the effectiveness of methylnaltrexone bromide oral tablets 450 mg for OIC in CNCP.

8. Safety

The clinical reviewer has recommended approval, and I agree with the recommendation. The reader is referred to the Clinical review by Dr. D. Zand, dated 03June2016 for complete information. I have summarized key findings below.

The submission of this NDA is based on the oral dosage form as an alternative to the SQ injection and relies on PK/PD modeling, allowing for extrapolation of data from the SQ program. As such, the sponsor did not provide long-term safety data for the oral formulation, rather, the majority of their safety data comes from a single 12-week, double-blind, placebo-controlled study (MNTX3201) which enrolled 804 patients with OIC and chronic, non-cancer pain. Patients received study drug or placebo once a day for Weeks 1 – 4, after which the study continued to be double-blind, placebo-controlled, however dosing of investigational agent (methylnaltrexone bromide or placebo) was as needed for the remaining 2 months of study. Safety data from this phase 3 study was supplemented by several phase 2, placebo-controlled, dose ranging studies in patients with OIC and chronic non-cancer pain, as well as a phase 1, double-blind, placebo controlled study comparing 2 oral formulations in the same patient population. This augmented safety database, the “oral placebo-controlled OIC pool”, was the primary analysis pool supporting the safety of oral methylnaltrexone bromide in OIC patients with chronic non-cancer pain. Table 10 below shows the extent of methylnaltrexone bromide exposure in the oral placebo-controlled OIC pool.

Table 11: Extent of Exposure: Oral Placebo-Controlled OIC Pool

Parameter	MNTX < 300 mg (N=327)	MNTX 300 mg (N=280)	MNTX 450 mg (N=385)	MNTX > 450 mg (N=65)	All MNTX (N=1057)	Placebo (N=344)
Duration of Drug Exposure (days)						
Mean (SD)	54.6 (28.8)	57.9 (28.5)	43.6 (33.9)	27.0 (6.3)	49.8 (31.0)	47.9 (31.4)
Median (min, max)	55.0 (1, 94)	79.5 (1, 91)	30.0 (1, 99)	28.0 (1, 36)	34.0 (1, 99)	31.0 (1, 91)
Duration of Drug Exposure by Category, n(%)						
≤1 day	5 (1.5)	4 (1.4)	82 (21.3)	1 (1.5)	92 (8.7)	37 (10.8)
>1 day - 7 days	6 (1.8)	6 (2.1)	9 (2.3)	1 (1.5)	22 (2.1)	7 (2.0)
>7 day - 14 days	8 (2.4)	10 (3.6)	14 (3.6)	2 (3.1)	34 (3.2)	13 (3.8)
>14 day - 28 days	61 (18.7)	48 (17.1)	53 (13.8)	32 (49.2)	194 (18.4)	75 (21.8)
>28 days - 56 days	84 (25.7)	56 (20.0)	70 (18.2)	29 (44.6)	239 (22.6)	65 (18.9)
>56 days - 84 days	134 (41.0)	121 (43.2)	129 (33.5)	0	384 (36.3)	128 (37.2)
>84 days	29 (8.9)	35 (12.5)	28 (7.3)	0	92 (8.7)	19 (5.5)

Source: Table 19, ISS

The extent of exposure to oral methylnaltrexone bromide does not meet the recommendations outlined in ICH E1A for drugs that are to be used chronically, which includes a recommendation that at least 100 patients should be exposed to the investigational drug at dosage levels intended for clinical use for a minimum of one-year (reference: *ICH E1A Guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions"* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf>). In addition, during a 2014 Advisory Committee to discuss the potential cardiovascular risk associated with PAMORA products in the treatment of OIC for chronic, non-cancer pain, the consensus of the advisory committee was that for PAMORA products in development, pre-approval general safety trials should be of sufficient duration to assess long term outcomes, generally 12 months or longer. The phase 3 clinical trial for oral methylnaltrexone bromide (MNTX3201) was complete prior to this advisory committee; however, and the Applicant is relying on long-term safety data from the approved Relistor® SC 12 mg injection. Systemic exposure, as measured by AUC, is comparable between the approved 12 mg QD SC dose and the proposed oral methylnaltrexone bromide dose of 450 mg QD (MNPK1117), and the C_{max} of the oral product is significantly less (20%) than that of the 12 mg SC MNTX injection. With this in mind, relying on long-term safety data from the subcutaneous formulation appears reasonable and the safety database for the oral formulation is acceptable.

In the oral placebo-controlled OIC pool, the incidence of treatment-emergent adverse events, drug-related adverse events, serious adverse events, and adverse events resulting in study discontinuation were similar across treatment arms and with methylnaltrexone bromide compared to placebo. This is shown in Table 11 below.

Table 12: Overview of Adverse Events: Oral Placebo-Controlled OIC Pool

Parameter	MNTX < 300 mg (N=327) n (%)	MNTX 300 mg (N=280) n (%)	MNTX 450 mg (N=385) n (%)	MNTX > 450 mg (N =65) n (%)	All MNTX (N=1057) n (%)	Placebo (N=344) n (%)
Number (%) of Subjects with						
TEAEs	168 (51.4)	159 (56.8)	194 (50.4)	34 (52.3)	555 (52.5)	183 (53.2)
Related TEAEs	49 (15.0)	65 (23.2)	88 (22.9)	9 (13.8)	211 (20.0)	68 (19.8)
Severe TEAEs	23 (7.0)	20 (7.1)	29 (7.5)	8 (12.3)	80 (7.6)	23 (6.7)
Deaths	0	0	1 (0.3)	0	1 (< 0.1)	0
SAEs	6 (1.8)	6 (2.1)	8 (2.1)	5 (7.7)	25 (2.4)	8 (2.3)
Related SAEs	0	0	0	1 (1.5)	1 (< 0.1)	0
TEAEs leading to permanent discontinuation of study drug	4 (1.2)	10 (3.6)	12 (3.1)	3 (4.6)	29 (2.7)	11 (3.2)

Source: Table 22 Integrated Safety Summary (ISS)

Note: The number of MNTX subjects who discontinued due to an AE is different in the disposition table (ST8.1; 28 subjects) and the AE tables (ST8.5.1.1 and ST8.5.2.2; 29 subjects). Subject 2201-008-0321 discontinued due to lack of efficacy, with an ongoing TEAE of increased constipation which was also considered a TEAE leading to discontinuation. For the disposition table this subject was only counted once with the primary cause of discontinuation, which was attributed to lack of efficacy.

Abbreviations: AE = adverse event; MNTX = methylnaltrexone; OIC = opioid-induced constipation; SAE = serious adverse event; and TEAE = treatment-emergent AE.

As is shown above, there was a single death during the entire oral methylnaltrexone bromide clinical development program. This occurred in a 56 year old male patient randomized to methylnaltrexone bromide 450mg in Study 2202, a phase 2 randomized, double-blind, placebo-controlled, parallel-group dose ranging study. The patient was found dead in his home by a family member on day 20 of the study, one day after contacting his daughter to say he was not feeling well. No autopsy was performed; however, the coroner's report noted the cause of death as natural due to atherosclerotic cardiovascular disease. The investigator's assessment was that this death was unlikely related to the study drug and more likely related to underlying cardiovascular disease, and the primary reviewer agreed with the investigator's assessment. This is discussed further below under special safety concerns, cardiovascular events.

During the 4-week, placebo-controlled, double blind portion of study MNTX 3201, the most common adverse events with oral MNTX 450mg were GI adverse events, specifically abdominal pain, nausea, and vomiting. These AEs occurred at a similar rate in patients receiving oral methylnaltrexone bromide compared to placebo. For the purposes of labeling, adverse events were defined as TEAEs reported by $\geq 2\%$ of subjects and more frequently with oral methylnaltrexone bromide than placebo during the 4-week double blind portion of Study 3201. In comparison to TEAEs presented in the labeling for Relistor® SC, adverse reactions of abdominal pain, nausea, diarrhea, and hyperhidrosis appeared to occur less frequently with the oral formulation, compared with the subcutaneous formulation, while abdominal distension and vomiting occurred more frequently with the oral formulation. This is shown in Table 11 below.

Table 13: Adverse reactions that occurred in $\geq 2\%$ of subjects and more frequently in the MNTX Treatment Group Than the Placebo Group in SC MNTX 3356 and in Oral MNTX Study 3201

	SC MNTX Study 3356		Oral MNTX Study 3201			
Preferred term	SC MNTX 12 mg QD 4 wks N = 150 N(%)	SC Placebo 4 wks N = 162 N(%)	Oral MNTX 450 mg QD – 4 wks N = 200 N(%)	Oral placebo 4 wks N = 201 N(%)	Oral MNTX 450 mg QD – 12 wks N = 200 N(%)	Oral Placebo 12 wks N = 200 N(%)
Abdominal Pain	31(20.7)	10(6.2)	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(6.0)	6(3.7)	9(4.5)	4(2.0)	16(8.0)	7(3.5)
Hyperhidrosis	9(6.0)	2(1.2)	5(2.5)	2(1.0)	6(3.0)	9(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 Distention	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(2.3)	2(1.2)	4(2.0)	1(0.5)	3(1.5)	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	2(1.0)	0	4(2.0)	1(0.5)

Source: Table 25 MNTX3201 Clinical Study Report

SC MNTX Study 3365 – 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

The Applicant proposes that the oral formulation is better tolerated, particularly related to adverse reactions possibly reflecting symptoms of opioid withdrawal, such as abdominal pain, diarrhea, and hyperhidrosis. However, when including abdominal distension and vomiting as adverse reactions possibly reflecting symptoms of opioid withdrawal, these reported differences in GI symptoms are less pronounced. This is further confounded by the fact that the proposed to-be-marketed formulation differs from that used in the phase 3 clinical trial. The only study with the to-be-marketed formulation was study MNOC1111, a single-dose, randomized, double-blind, placebo controlled study to compare the PK and tolerability of the (b) (4) formulation used in Study MNTX 3201 with the to-be-marketed formulation. According to the primary reviewer's assessment, there was a higher incidence of GI related adverse events in patients receiving the to-be-marketed formulation, compared with the phase 3 study formulation. Specifically, 7 patients using the to-be-marketed formulation experienced 12 GI related adverse events, compared to 2 patients experiencing 4 such adverse events with the phase 3 study formulation. This study was small (approximately 37 patients per treatment arm), however, and patients received only a single-dose of drug product, so these findings must be taken in context.

Special Safety Concerns:

The primary safety concern associated with the peripherally acting mu opioid receptor antagonist (PAMORA) class are CV adverse events, bowel perforation, and opioid withdrawal.

Cardiovascular adverse events:

A potential CV safety signal (myocardial ischemia) was originally observed in a long-term safety study of alvimopan, a PAMORA approved in 2008 for the treatment of post-op ileus.

Specifically, an imbalance in myocardial infarctions was observed in a 52 week randomized controlled, safety trial. Patients were randomized 2:1 to alvimopan and placebo, and there were 7 myocardial infarctions reported with alvimopam, including 1 cardiac death, compared with zero in the placebo arm.

The clinical development program for Relistor® SQ for OIC in chronic, non-cancer pain included a single 4-week randomized, double-blind, placebo controlled clinical trial. There was no CV imbalance found during the controlled clinical trial, however, this study was of limited duration. An open-label, uncontrolled 48-week extension study was completed and included 1034 patients. There were 7 investigator reports of CV events or death in this study, however the lack of a control group made interpretation of these events challenging. This application was initially CR'd (in 2012) and the Sponsor was advised to conduct a cardiovascular outcome trial (CVOT) premarketing, to assess for potential cardiovascular risk. Ultimately, an Advisory Committee was held in June 2014 to discuss a potential cardiovascular risk associated with products in the class of PAMORA and the necessity, timing, design and size of CVOTs to support approval of products in this class for the proposed indication of opioid-induced constipation (OIC) in patients taking opioids for chronic non-cancer pain. Consensus of the Advisory Committee was that for products in development, pre-approval general safety trials should be of sufficient duration to assess long term outcomes (e.g., 12 months), ideally controlled, but that a dedicated premarket CVOT was not supported.

In addition, the committee stated that post-marketing observational studies may also be conducted (post-approval) and that appropriate measures should be taken to enrich them with high cardiovascular risk patients. Supplemental NDA 21964 (Relistor® SQ) and NDA 204760 (Movantik®, naloxegol) were approved in September 2014, both with a PMR to conduct a postmarketing observational study to assess for MACE.

There was no signal for cardiovascular adverse events identified during the oral methylnaltrexone bromide clinical development program. Cardiac related adverse events were infrequent and generally mild and not considered related to study drug. There was a single death from cardiac arrest during the entire clinical development program which is summarized below. There were no other SAEs of myocardial infarction, cardiac failure congestive, or cerebrovascular accident.

Subject 2202-016-0684: This subject was a 56-year-old man with a medical history of cervical and lumbar degenerative disc disease, chronic obstructive pulmonary disease, and heavy smoking; he was randomly assigned to the methylnaltrexone bromide 450mg in Study 2202 on 18 Mar 2008. During the screening visit, the subject had a low heart rate (47 beats per minute). The screening electrocardiogram showed sinus bradycardia and a nonspecific intraventricular conduction delay. On (b) (6) (Day 19 of the study) the patient contacted his daughter stating that he was not feeling well and one day later he was found dead. Concomitant medications included milk of magnesia, Amitiza, and approximately 71.4 mg of morphine equivalent pain medications for back pain. The coroner's report cited the cause of death as due to atherosclerotic cardiovascular disease. No autopsy was performed, and the death was considered not related to study drug by the investigator.

In summary, no new safety signal for cardiovascular events was identified during the clinical development program for oral methylnaltrexone bromide. However, as the potential cardiovascular risk associated with products in the class of PAMORA has not yet been fully assessed in ongoing postmarketing observational studies, an observational study is needed

to evaluate for a signal of risk for MACE in patients receiving methylnaltrexone bromide oral tablets for OIC in CNCP.

Gastrointestinal perforation:

Gastrointestinal perforations, including some resulting in death, have been reported in the post-marketing setting with the use of Relistor® SC, specifically in patients with OIC and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, infiltrative gastrointestinal tract malignancies, peritoneal metastases). This adverse reaction finding led to a labeling update on July 23, 2010, and gastrointestinal perforation is currently listed in the Warnings and Precautions

No cases of GI perforation were identified during the oral methylnaltrexone bromide clinical development program, and Dr. Zand concluded that no new safety signals or patterns have emerged with oral methylnaltrexone bromide that require further labeling modification.

Opioid withdrawal:

The potential of oral methylnaltrexone bromide to cause opioid withdrawal symptoms or impact analgesia was evaluated by assessments of potential opioid withdrawal symptoms recorded as AEs during treatment, analysis of subjects who met the Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (DSM-V) criteria for opioid withdrawal, analyses of opioid withdrawal questionnaires, and review of subject pain scores and opioid use throughout the clinical development program. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) was consulted to comment on the adequacy of the Applicants opioid withdrawal assessments and whether there was evidence of opioid withdrawal in patients receiving methylnaltrexone bromide compared to placebo in study MNTX3201.

The DAAAP came to the following 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 suggest that the risk for opioid withdrawal with methylnaltrexone bromide oral tablets is similar to that with Relistor® SC and the Applicant's proposed labeling is acceptable.
- 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.

Based on the review by the clinical reviewer and the reviewer from the DAAAP, it does not appear that the risk for opioid withdrawal with methylnaltrexone bromide oral tablets is different than that currently labeled for Relistor® SC. The reader is referred to the Response to Consultation Request by Dr. E. Kilgore from DAAAP, dated 21March2016, for complete information.

In conclusion, the safety profile of oral methylnaltrexone bromide was comparable to that of the approved formulation of Relistor® SC and may have improved tolerability related to GI adverse events. No signal for MACE was identified during this clinical development program; however, a post-marketing requirement for an observational study to evaluate for MACE, similar to that of the approved formulation Relistor® SC, is needed to determine if there is a signal for cardiovascular events in patients receiving PAMORAs for chronic, non-cancer pain.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application. There were no decisional issues that required input from an Advisory Committee during this review cycle.

10. Pediatrics

Oral methylnaltrexone bromide has not been evaluated in a pediatric OIC population. The Applicant submitted a request for a waiver in pediatric patients 0 through 17 years due to the low number of pediatric patients with chronic opioid use for non-cancer indications, and thus few patients with OIC associated with chronic opioid use.

As noted in Dr. Hausman's review, *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 PAMORA under development for treatment of OIC-associated constipation; DPMH review, IND 107475, September 18, 2015).*

The Applicant's full waiver request was granted by the Pediatric Review Committee (PeRC) on 17February2016.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations

Five clinical sites were selected for inspection, based on high enrollment rates, high number of INDs, and/or history of complaints. Four sites were classified as NAI (no action indicated) and one site was classified as VAI (voluntary action indicated).

The Clinical reviewer noted in her review that Clinical Site 025 was issued a VAI for randomizing a patient to placebo who should have been excluded due to use of laxative within the 72 hours after a bowel movement. This was noted in the NDA as a protocol violation and the clinical investigator adequately responded to the inspection findings. This violation is considered minor and would not be expected to affect data integrity. OSI determined that the data generated by this site was acceptable for use.

The reader is referred to the OSI review by Dr. S. Leibenhaut, dated 20January2016, for details.

12. Labeling

Proprietary Name:

The Office of Medication Error Prevention and Risk Management determined that the proposed proprietary name Relistor is acceptable. The reader is referred to the Proprietary Name review by Drs. S. Abraham, K. Worthy, and L. Merchant, dated 02July2015.

Specific Labeling Issues:

Information on Relistor® (methylnaltrexone bromide) tablets is proposed to be added to the approved label for Relistor® injection. Labeling negotiations were ongoing at the time of this document. For final labeling agreements, the reader is referred to the approved product label. The key changes and recommended changes to the labeling at the time of this review are summarized below.

Highlights:

- The dosage forms and strengths were updated to accurately reflect the Naming of Drug Products Containing Salt Drug Substances guidance, specifically, the salt (methylnaltrexone bromide) is retained to be consistent with other dosage forms of the same active ingredient (the subcutaneous formulation).

Section 2 Dosage and Administration

- Section 2.4: The dosage in patients with renal impairment was updated to include a dose reduction in patients with moderate renal impairment, in addition to severe renal impairment.
- Section 2.5: Recommendations were added to adjust the dosage of RELISTOR injection for those with severe hepatic impairment, specifically:

Table 3: Weight-Based Dosing in Severe Hepatic Impairment of RELISTOR Injection and Corresponding Injection Volume for Adult Patients with OIC and Chronic Non-Cancer Pain		
Weight of Adult Patient	Subcutaneous Dose	Injection Volume
Less than 38 kg	0.075 mg/kg	See below*
38 kg to less than 62 kg	4 mg	0.2 mL
62 kg to 114 kg	6 mg	0.3 mL
More than 114 kg	0.075 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.

Section 3 Dosage Forms and Strengths

- The dosage forms and strengths were updated to accurately reflect the Naming of Drug Products Containing Salt Drug Substances guidance, specifically, the salt (methylnaltrexone bromide) is retained to be consistent with other dosage forms of the same active ingredient (the subcutaneous formulation).

Section 6 Adverse Reactions

- Table 4 was revised to reflect adverse reactions (ARs) which occurred during the 4 week double blind period, as was done with the subcutaneous formulation AR table.

A footnote was added to the table, including all related terms to abdominal pain which are reflected in the abdominal pain category in the table.

- Table 5 was updated to include a footnote, including all related terms to abdominal pain which are reflected in the abdominal pain category in the table.

Section 8 Use in Specific Populations

- Section 8.1: The “Pregnancy” subsection of Relistor labeling was structured in the PLLR format to include the “Risk Summary” and “Data” subsections.14
- Section 8.2: The “Lactation” subsection of Relistor labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections
- Section 8.3: As there is no concern for infertility in humans, this section was removed and details about animal fertility studies were kept in section 13.1.
- Section 8.5: Wording was revised to be consistent with 21 CFR 201.57, Geriatric Use.
- Section 8.6: The recommendations for patients with renal impairment were updated to include a recommendation for a dosage adjustment in patients with moderate, as well as severe, renal impairment.
- Section 8.7: The recommendations for patients with hepatic impairment were updated.

Section 11 Description

- An equivalency statement was added clearly identifying the strengths of the salt and the active moiety

Section 12 Clinical Pharmacology

- A statement was added the first time the IV route in humans is mentioned stating that Relistor is not approved for intravenous use.
- Language was added to Section 12.3 Pharmacokinetics, *The absolute bioavailability of oral methylnaltrexone bromide has not been determined. The C_{max} and AUC in healthy subjects was 48 (b) (4) ng/mL and 382 ng.hr/mL following single 450 -mg dose of RELISTOR tablets. The exposure in the OIC patient population was approximately 27% lower than that in healthy subjects.*
- A (b) (4) was removed (b) (4)
- Revisions were made to describe the elimination of methylnaltrexone as, *Following oral administration of a single 450-mg dose of RELISTOR tablets, concentrations of methylnaltrexone decline in a (b) (4) manner with a terminal half-life ($t_{1/2}$) of approximately 15 hours.*
- A statement was added regarding the metabolism stating, *Systemic exposures of methylnaltrexone metabolites after oral administration of a single 450 mg dose of RELISTOR tablets are greater than the systemic exposure of methylnaltrexone metabolites after subcutaneous administration of a single 12 mg dose of RELISTOR injection. Subcutaneous administration is not subject to first-pass hepatic metabolism prior to appearance in the systemic circulation.*
- A statement stating (b) (4) was removed (b) (4)
- A statement was added to the excretion section stating, No mass balance clinical studies were conducted with oral administration of methylnaltrexone bromide. However, following once daily dosing of 450 mg RELISTOR tablets for one week, the

percentage of dose recovered in the urine as the parent methylnaltrexone was low (approximately 1% on both Day 1 and Day 7).

- The renal impairment section was revised to include the following language, *Administration of a single subcutaneous dose of 0.3 mg/kg of RELISTOR injection in subjects with varying degrees of renal impairment (8 subjects each cohort) resulted in a 1.3-, 1.7^{(b) (4)} and 1.9-fold higher AUC_{0-∞} of methylnaltrexone, respectively, compared to 8 subjects with normal renal function [see Dosage and Administration (2.4)]. The mean C_{max} did not change significantly with renal impairment. No studies were performed in patients with end-stage renal impairment requiring dialysis.*
- The hepatic impairment section was revised to include the following language, *Administration of a single 450-mg dose of RELISTOR tablets in subjects with mild, moderate, and severe hepatic impairment (6 subjects each of Child-Pugh Class A, B, and C) resulted in a 1.7^{(b) (4)}-, 4.8- and 3.8-fold higher C_{max} of methylnaltrexone, respectively, compared to 6 subjects with normal liver function. The AUC_{0-∞} was comparable between healthy subjects and subjects with mild hepatic impairment, but increased approximately 2.1-fold in subjects with moderate and severe hepatic impairment [see Dosage and Administration (2.5)].*
- The effect of methylnaltrexone on transporters section was updated to include information for the metabolites.

Section 13 Nonclinical Toxicology

- Statements were added throughout providing an equivalency statement for nonclinical studies to the maximum recommended human dose (MRHD)

Section 14 Clinical Studies

- ^{(b) (4)} was removed ^{(b) (4)}
- Clarifying changes were made to the table summarizing the results of the responder endpoint, for example, the definition of a responder was added as a footnote to the table. In addition, ^{(b) (4)} was removed ^{(b) (4)}

Section 17 Patient Counseling Information

- The "Patient Counseling Information" subsection was formatted to include a review of information that had been presented in sections 8.1 and 8.2.

Labeling Conclusions:

In addition to the review team and the DAAAP consultant, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis who found the prescribing information, carton labeling and container labels acceptable from a medication error perspective. At the time of this review, labeling negotiations are still ongoing, so the reader is referred to the approved product label for the final agreed upon label.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend that Relistor® (methylnaltrexone bromide) oral tablets 450 mg be approved for the indication of treatment of opioid- induced constipation (OIC) in adults with chronic non-cancer pain

Risk Benefit Assessment

Approvability of NDA 208271 is based on the development program of an oral methylnaltrexone bromide tablet as an alternative to the approved subcutaneous formulation. In support of this NDA, the Applicant conducted a single adequate and well controlled phase 3 study of oral methylnaltrexone bromide, MNTX3201. In addition to the phase 3 study, the Applicant submitted multiple clinical pharmacology studies, allowing extrapolation of efficacy results from studies for the approved Relistor® to support approval for the oral dosage form provided data characterizing the pharmacokinetic (PK) relationship of subcutaneous (SC), intravenous and oral dosage forms.

A major theme in the review of the efficacy for this application was whether the results of the phase 3 trial (MNTX3201) could support the approval of methylnaltrexone bromide oral tablets, given that the Agency disagreed with the prespecified primary endpoint. Ultimately it was decided that the responder secondary endpoint could be reviewed and would be considered as the relevant endpoint for determination of approvability. The statistical review team determined the results for Relistor 450mg to be statistically significant compared to placebo ($p=0.005$ and $p=0.008$, Sponsor's and reviewer's assessments, respectively). Similarly, the clinical reviewer recommended that methylnaltrexone bromide tablets 450 mg be approved for the treatment of OIC in adult patients with chronic, non-cancer pain based on the Applicant's demonstration of efficacy for their pre-specified primary endpoint at the proposed dose for marketing and the demonstration of statistical significance over placebo with the Applicant's key secondary responder endpoint. The clinical reviewer concluded that "while there were limitations to the data provided, the oral formulation of methylnaltrexone bromide may have slightly better tolerability, and there are benefits to the availability of an oral formulation for patients who may not be able to use the subcutaneous formulation."

The quality reviewers concluded that the applicant provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Similarly, the nonclinical review team concluded that the nonclinical safety of oral methylnaltrexone has been adequately addressed, and no nonclinical approval issues were identified. Finally, the clinical pharmacology review team considers the submission acceptable from a clinical pharmacology standpoint

Based on the data provided, I agree with the reviewers that the data submitted in the NDA support the approval of methylnaltrexone bromide 450 mg for the treatment of OIC in adult patients with chronic, non-cancer pain. In addition, no new safety signals were identified for methylnaltrexone bromide tablets during the clinical studies, and the benefits of the oral tablet formulation outweigh the risks associated with the use of this product.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing requirement has been agreed to with the Applicant with the following timelines.

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.

Final Protocol Submission: 07/2017

Study/Trial Completion: 04/2024

Final Report Submission: 07/2025

Recommended Comments to Applicant

No additional comments to the Applicant are recommended.

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

/s/

LAURIE B MULDOWNNEY
06/28/2016